

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

76-110

Generic Name: Toremide Tablets,
5mg, 10mg, 20mg. and 100mg

Sponsor: TEVA Pharmaceuticals USA

Approval Date: May 14, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
76-023**

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-110

APPROVAL LETTER

ANDA 76-110

MAY 14 2002

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 1, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Torsemide Tablets, 5 mg, 10 mg, 20 mg, and 100 mg.

Reference is also made to your amendments dated May 16, 2001, and April 16, 2002.

The listed drug product (RLD) referenced in your application, Demadex Tablets of Hoffmann La Roche, Inc., is subject to a period of patent protection (U.S. Patent No. RE 34,672, the '672 patent) which expires on August 11, 2006. Your application contains a patent certification to this patent under Section 505(j)(2)(A)(vii)(IV) of the Act. This certification states that the patent will not be infringed by your manufacture, use, or sale of this drug product, or that the patent is invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of the ANDA shall be made effective immediately unless an action is brought for infringement of the patent before the expiration of forty-five days from the date the notices provided under paragraph (2)(B)(i) are received. You have notified FDA that TEVA Pharmaceuticals USA (TEVA) has complied with the requirements of Section 505(j)(2)(B) of the Act, and that no action for infringement of the '672 patent was brought against TEVA 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, 20 mg, and

100 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Demadex® Tablets, 5 mg, 10 mg, 20 mg, and 100 mg, respectively, of Hoffmann La Roche, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Furthermore, we note that TEVA is the first applicant to submit a substantially complete ANDA with a Paragraph IV Certification for all strengths of this drug product. Therefore, with this approval TEVA is eligible for 180-days of market exclusivity for this drug product as provided for under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j)(5)(B)(iv) of the Act. Such exclusivity will begin to run either from the date TEVA begins commercial marketing of the drug product, or in the absence of marketing, from the date of a decision of a court finding the patent invalid or not infringed, whichever event occurs earlier [Section 505(j)(5)(B)(iv)].

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product, or the date of a decision of the court holding the relevant patent invalid, unenforceable or not infringed.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

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

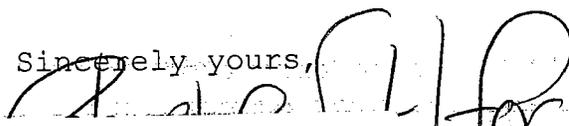
Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to cooperate with the agency to satisfactorily resolve any deficiencies that may be identified.

Sincerely yours,


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Gary Bienler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

for
5/14/2002

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-110

FINAL PRINTED LABELING(S)

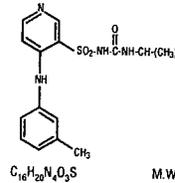


7127
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TORSEMIDE TABLETS, 5 mg, 10 mg, 20 mg and 100 mg Rx only

DESCRIPTION

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



M.W. 348.43



MAY 14 2002

Torsemide has a pKa of 7.1.

Torsemide is a white to off-white crystalline powder. The tablets for oral administration also contain croscopovidone, 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 that 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-rin 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 sulfonyleureas.

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.

DECREASE HEPATIC CLEARANCE BY 50% IN PATIENTS WITH CIRRHOSIS.

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 furosemide 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.

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In controlled studies in the United States, furosemide 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 furosemide (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 furosemide 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 furosemide.

PRECAUTIONS

Laboratory Values

Potassium: See statement in **WARNINGS**.

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

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

Blood Urea Nitrogen (BUN), Creatinine and Uric Acid: Furosemide produces small dose-related increases in each of these laboratory values. In hypertensive patients who received 10 mg of furosemide 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 furosemide, but its incidence has been similar to that seen in patients receiving placebo.

Glucose: Hypertensive patients who received 10 mg of daily furosemide 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 furosemide were associated with increases in total plasma cholesterol of 4, 4, and 8 mg/dL (0.10 to 0.20 mmol/L), respectively. The changes subsided during chronic therapy.

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

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

Other: In long-term studies in hypertensive patients, furosemide 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, furosemide has been administered together with beta-blockers, ACE inhibitors, and calcium-channel blockers. In patients with congestive heart failure, furosemide 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.

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

Because furosemide and salicylates compete for secretion by renal tubules, patients receiving high doses of salicylates may experience salicylate toxicity when furosemide is concomitantly administered. Also, although possible interactions between furosemide 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 one 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/m² 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/m² 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 pelvis. Some of these calculi have been dissolved, and hypercalciuria has been reported to have decreased, when chlorothiazide has been coadministered along with the loop diuretic. In other premature neonates with hyaline membrane disease, another loop diuretic has been reported to increase the risk of persistent patent ductus arteriosus, possibly through a prostaglandin-E-mediated process. The use of torsemide in such patients has not been studied.

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

ADVERSE REACTIONS

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

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

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

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

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

	Torsemide (N=564)	Placebo (N=274)
Headache	7.3	9.1
Excessive Urination	6.7	2.2
Dizziness	3.2	4.0
Rhinitis	2.8	2.2
Asthenia	2.0	1.5
Diarrhea	2.0	1.1
ECG Abnormality	2.0	0.4
Cough increase	2.0	1.5
Constipation	1.8	0.7
Nausea	1.8	0.7
Arthralgia	1.8	0.7
Dyspepsia	1.6	0.7
Sore Throat	1.6	1.5
Myalgia	1.2	0.4
Chest Pain	1.2	1.8
Insomnia	1.1	1.1
Edema	1.1	0.4
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, stent 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 statement in **WARNINGS**.

OVERDOSAGE

There is no human experience with overdoses of torsemide, but the signs and symptoms of overdosage can be anticipated to be those of excessive pharmacologic effect: dehydration, hypovolemia, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, and hemoconcentration. Treatment of overdosage should consist of fluid and electrolyte replacement. Laboratory determinations of serum levels of torsemide and its metabolites are not widely available.

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

DOSAGE AND ADMINISTRATION

General: Torsemide tablets may be given at any time in relation to a meal, as convenient. Special dosage adjustment in 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

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 the table below.

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

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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 statement in **WARNINGS**.

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

General: Torsemide tablets may be given at any time in relation to a meal, as convenient. Special dosage adjustment in 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 for oral administration is available as:

5 mg - white to off-white, oval shaped tablet, scored and debossed "9" and "3" on each side of the score, and debossed "7127" on the other side. They are available in bottles of 100.

10 mg - white to off-white, oval shaped tablet, scored and debossed "9" and "3" on each side of the score, and debossed "7128" on the other side. They are available in bottles of 100 and 500.

20 mg - white to off-white, oval shaped tablet, scored and debossed "9" and "3" on each side of the score, and debossed "7129" on the other side. They are available in bottles of 100 and 500.

100 mg - white to off-white, oval shaped tablet, scored and debossed "9" and "3" on each side of the score, and debossed "7130" on the other side. They are available in bottles of 100 and 500.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18950

Iss. 8/2001

Mango

ANDA # 76-110
TORSEMIDE TABLETS, 100 mg
Container Label
500's

NDC 0093-7130-05

TORSEMIDE
Tablets
100 mg

Each tablet contains:
Torsemide 100 mg

MAY 14 2002
Rx only



TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



NDC 0093-7130-05

TORSEMIDE
Tablets
100 mg

Each tablet contains:
Torsemide 100 mg

MAY 14 2002
Rx only



TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



NDC 0093-7130-05

TORSEMIDE
Tablets
100 mg

Each tablet contains:
Torsemide 100 mg

MAY 14 2002
Rx only



TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



Margo

ANDA # 76-110
TORSEMIDE TABLETS, 100 mg
Container Label
100's

NDC 0093-7130-01

**TORSEMIDE
Tablets
100 mg**

Each tablet contains:
Torsemide 100 mg

Rx only
MAY 14 2002



TEVA

NDC 0093-7130-01

**TORSEMIDE
Tablets
100 mg**

Each tablet contains:
Torsemide 100 mg

Rx only
MAY 14 2002



TEVA

NDC 0093-7130-01

**TORSEMIDE
Tablets
100 mg**

Each tablet contains:
Torsemide 100 mg

Rx only
MAY 14 2002



TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Salesville, PA 18960

APPROVED



Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Salesville, PA 18960

APPROVED



Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Salesville, PA 18960

APPROVED



Mang

ANDA # 76-110
TORSEMIDE TABLETS, 20 mg
Container Label
500's

Usual Dosage: See package insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F). Do not freeze.
Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
TP Iss. 8/2001
Manufactured By: TEVA PHARMACEUTICAL IND. LTD., Jerusalem, 91010, Israel
Manufactured For: TEVA PHARMACEUTICALS USA Sellersville, PA 19980



NDC 0093-7129-05

TORSEMIDE
Tablets
20 mg

Each tablet contains:
Torsemide 20 mg

MAY 14 2002
Rx only



Usual Dosage: See package insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F). Do not freeze.
Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
TP Iss. 8/2001
Manufactured By: TEVA PHARMACEUTICAL IND. LTD., Jerusalem, 91010, Israel
Manufactured For: TEVA PHARMACEUTICALS USA Sellersville, PA 19980



NDC 0093-7129-05

TORSEMIDE
Tablets
20 mg

Each tablet contains:
Torsemide 20 mg

MAY 14 2002
Rx only



Usual Dosage: See package insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F). Do not freeze.
Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
TP Iss. 8/2001
Manufactured By: TEVA PHARMACEUTICAL IND. LTD., Jerusalem, 91010, Israel
Manufactured For: TEVA PHARMACEUTICALS USA Sellersville, PA 19980



NDC 0093-7129-05

TORSEMIDE
Tablets
20 mg

Each tablet contains:
Torsemide 20 mg

MAY 14 2002
Rx only



Martín

ANDA # 76-110
TORSEMIDE TABLETS, 20 mg
Container Label
100's

NDC 0093-7129-01

TORSEMIDE
Tablets
20 mg

Each tablet contains:
Torsemide 20 mg

Rx only
MAY 14 2002

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



NDC 0093-7129-01

TORSEMIDE
Tablets
20 mg

Each tablet contains:
Torsemide 20 mg

Rx only
MAY 14 2002

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



NDC 0093-7129-01

TORSEMIDE
Tablets
20 mg

Each tablet contains:
Torsemide 20 mg

Rx only
MAY 14 2002

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Iss. 8/2001

Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



NDC 0093-7128-05

TORSEMIDE Tablets 10 mg

Each tablet contains:
Torsemide 10 mg

MAY 14 2002
Rx only



Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP 155, 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Janssen, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



APPROVED

NDC 0093-7128-01
TORSEMIDE Tablets
10 mg

Each tablet contains:
Torsemide 10 mg

MAY 14 2002
Rx only



Usual Dosage: See package insert for full prescribing information.

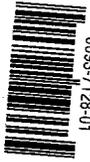
Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP 155, 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Janssen, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



APPROVED

TEVA

NDC 0093-7127-01
TORSEMIDE Tablets
5 mg

Each tablet contains:
Torsemide 5 mg

MAY 14 2002
Rx only



Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

Dispense in a light, light-resistant container as defined in the USP with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP 155, 8/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Janssen, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



APPROVED

14 pages redacted from this section of
the approval package consisted of draft labeling

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-110

CSO LABELING REVIEW(S)

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

ANDA Number: 76-110
 Date of Submission: September 4, 2001
 Applicant's Name: TEVA Pharmaceuticals, USA
 Established Name: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg.

APPROVAL SUMMARY

1. **Do you have 12 Final Printed Labels and Labeling?** Yes
2. **CONTAINER Labels:** Bottles of 100 and 500 tablets
Satisfactory in **final print** as of the September 4, 2001 submission
3. **PROFESSIONAL PACKAGE INSERT Labeling:**
Satisfactory in **final print** as of the September 4, 2001 submission
4. Revisions needed post-approval: None
5. **Patent Data – NDA 20-136**

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

Exclusivity Data– NDA 20-136

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

BASIS OF APPROVAL:

Was this approval based upon a petition? No
 What is the RLD on the 356(h) form: Demadex®
 NDA Number: N 20-136/S-011
 NDA Drug Name: Demadex®
 NDA Firm: Boehringer Mannheim Corporation; N 20-136/S-011; Approved February 13, 1998; Revised December 1997.)
 Date of Approval of NDA Insert and supplement: February 13, 1998; NDA 20-136/S-011
 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, Demadex®

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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 24		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			
<i>PROPRIETARY NAME</i>			
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
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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	
<i>LABELING</i>			
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	
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 (p. #) 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 p. # 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		

FOR THE RECORD:

- 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 the most recently approved labeling for the RLD.
- 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

- Storage/Dispensing Conditions:
 NDA: Store at 15 - 30°C (59 – 86°F) Dispense in tight containers as defined in USP/NF.
 ANDA: Store at controlled room temperature 15 - 30°C (59 – 86°F). Dispense in well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).
 Do not freeze
- Product Line:
 The innovator markets their product as 5mg, 10mg, 20mg and 100mg strength in bottles containing 100 and tablets and unit dose packages of 100.

The applicant proposes to market their product in 5mg in bottles of 100 and 10mg, 20mg and 100mg

strengths in bottles containing 100 and 500 tablets.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page. See pages 70, Vol. A. 2.1 and pg. 134 in vol. B. 1.1.

6. All manufacturing will be performed by TEVA Pharmaceuticals, USA (See pg. 287 in vol. B.1.1)

7. Container/Closure:

This product will be packaged in white HDPE bottles. The 100 count bottles will utilize both a CRC. The bottles of 500 will only utilize non-CRC caps. See pages 558, 559 and 560 in vol. B. 1.2 and page 326 in Vol. B. 2.2.

8. The tablet imprintings **have been accurately** described in the HOW SUPPLIED section. (see pages 704, 707 and 710 in vol. B. 1.2 AND page 406 in vol. B 2.2.

Date of Review: 9/24/01

Date of Submission: 9/4/01

Primary Reviewer: Jim Barlow

Date: *J Barlow*

Team Leader: John Grace

Date:

ISI

9/25/2001

cc:

ANDA: 76-110

DUP/DIVISION FILE

HFD-613/JBarlow/JGrace (no cc)

Review

**APPEARS THIS WAY
ON ORIGINAL**

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

ANDA Number: 76-110 Date of Submission: February 1, 2001 & February 23, 2001
Applicant's Name: TEVA Pharmaceuticals, USA
Established Name: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg.

Labeling Deficiencies:

1. **CONTAINER – (5 mg, 10 mg and 20 mg)** Bottles of 100 and 500 tablets
Satisfactory in **draft** as of the February 1, 2001 submission.

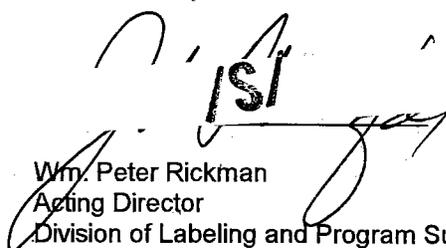
2. **CONTAINER – (100 mg)** Bottles of 100 and 500 tablets
Satisfactory in **draft** as of the February 23, 2001 submission.

3. **PACKAGE INSERT**
Please refer to the attached mock-up copy of your draft insert labeling for all of the requested labeling revisions.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


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

Attachment: Copy of firm's mocked-up insert labeling.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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 24		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			
<i>PROPRIETARY NAME</i>			
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
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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	
<i>LABELING</i>			
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	
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 (p. #) 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 p. # 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		

FOR THE RECORD:

- 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 the most recently approved labeling for the RLD.
- Patent/ Exclusivities:
Patent #RE34672 expires on August 11, 2006. The firm is filing paragraph IV and intends on marketing this product upon its approval.
- Storage/Dispensing Conditions:
NDA: Store at 15 - 30°C (59 – 86°F) Dispense in tight containers as defined in USP/NF.
ANDA: Store at controlled room temperature 15 - 30°C (59 – 86°F). Dispense in well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).
- Product Line:
The innovator markets their product as 5mg, 10mg, 20mg and 100mg strength in bottles containing 100 and tablets and unit dose packages of 100.

The applicant proposes to market their product in 5mg in bottles of 100 and 10mg, 20mg and 100mg strengths in bottles containing 100 and 500 tablets.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page. See pages 70, Vol. A. 2.1 and pg. 134 in vol. B. 1.1.

6. All manufacturing will be performed by TEVA Pharmaceuticals, USA (See pg. 287 in vol. B.1.1)

7. Container/Closure:

This product will be packaged in white HDPE bottles. The 100 count bottles will utilize both a CRC. The bottles of 500 will only utilize non-CRC caps. See pages 558, 559 and 560 in vol. B. 1.2 and page 326 in Vol. B. 2.2.

8. The tablet imprintings **have been accurately** described in the HOW SUPPLIED section. (see pages 704, 707 and 710 in vol. B. 1.2 AND page 406 in vol. B 2.2.

Date of Review: 3/30/01

Date of Submission: 2/23/01

Primary Reviewer: Jim Barlow

Date: 4/3/01

Team Leader: John Grace

Date:

cc:

ANDA: 76-110

DUP/DIVISION FILE

HFD-613/JBarlow/JGrace (no cc)

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Review

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-110

**MEDICAL OFFICER
REVIEW(S)**

Attachment I/II to ANDA 76-110

MEDICAL OFFICER REVIEW

January 9, 2001

CD #00-392

CD #00-532

CD #01-003

Drug Product: Torsemide 5, 10, 20, and 100 mg

From: Teva Pharmaceutical USA (#00-392, #01-003)
~~_____~~ (#00-532)

Re: Reference Listed Drug strength for bioequivalence study

The Office of Generic Drugs has received correspondence from two parties asking that the reference listed drug, currently the 200 mg tablet, be changed because of safety concerns. Teva Pharmaceuticals USA is asking that the 20 mg tablet be used for comparison of the generic and innovator drug products. _____ is proposing that the bioequivalence studies be conducted using the 10 mg strength tablets. Both parties provide the same justification for the proposed change and therefore, both controlled documents will be reviewed at the same time.

Torsemide (Demadex®, Roche Laboratories) is a loop diuretic of the pyridine-sulfonylurea class. The tablets have 80% bioavailability and induce onset of diuresis within 1 hour of ingestion. The peak effect occurs in the first or second hour and diuresis lasts about 6 to 8 hours. Demadex ® is indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease and for the treatment of hypertension either used alone or in combination with other antihypertensive agents. The usual initial dose recommended in the labeling is 10 or 20 mg for patients with congestive heart failure, 20 mg for patients with chronic renal failure, 5 or 10 mg for hepatic cirrhosis, and 5 mg once daily for the treatment of hypertension. For patients with congestive heart failure (CHF) and chronic renal failure who do not respond to the 20 mg dose, the dose can be titrated up to 200 mg until a response is obtained. For patients with hepatic cirrhosis, the maximum dose studied is 40 mg. If patients with hypertension do not respond to a dose of 10 mg, it is recommended that an additional antihypertensive agent should be added to the treatment regimen. The higher doses recommended for patients with congestive heart failure and chronic renal failure are necessary because the kidney is relatively resistant to diuresis.

_____ bases their justification on concern that running bioequivalence studies with 100 mg doses in healthy subjects could be dangerous and result in serious electrolyte imbalance and marked volume depletion with its associated symptoms of hypotension, syncope, tachycardia, vomiting, headaches, etc. In addition, they point out that ototoxicity has been reported with Demadex®, although this is rare. They note that

Cmax and AUC are dose proportional over the range of 2.5 mg to 200 mg after oral administration. Teva Pharmaceuticals USA submitted two papers that discuss administration of Torsemide (torasemide) in healthy subjects:

1. "Study of the Tolerance and Diuretic Properties of Torasemide Following Oral or Intravenous Administration to Healthy Volunteers", Lambe, R., et. al., European Journal of Clinical Pharmacology 31(suppl.): 9-14, 1986.
2. "Torasemide: An Update of its Pharmacologic Properties and Therapeutic Efficacy", Dunn, C. J., et. al., Drugs 49(1): 121-142, 1995.

The pertinent observations in these two publications are as follows:

Lambe, et.al. conducted a dose escalation study in healthy volunteers. At the highest oral doses (80 mg and 100 mg) cramps in the knees, calves, and feet were reported by a number of volunteers. Muscle cramps have been previously reported in association with furosemide and bumetanide therapy. Following the 40 mg oral dose, several subjects complained of suprapubic discomfort and urgency, which was relieved by micturation.

Dunn et. al. reviewed the literature available in 1995 for this drug product. They presented summary information that indicates that oral torasemide (torsemide) 5 to 20 mg/day has shown efficacy equivalent to that of oral furosemide 40 mg/day, over periods ranging from 8 days to 14 weeks in the management of chronic CHF. Under the heading of "Tolerability", the authors report that "adverse effects observed during treatment with torasemide are usually mild and transient in nature and include fatigue, dizziness, headache, muscle cramps, lower back pain, skin rash, nausea and orthostatic hypotension."

Conclusion and Recommendation

The data presented in these two controlled documents supports the request to use a lower dose in the conduct of bioequivalence comparisons of generic drug products and Demadex®. Since the range of initial dosage is 5 to 20 mg and this dosage has been determined to provide similar efficacy to oral furosemide 40 mg/day, it is recommended that the reference listed drug be changed to the 20 mg tablet.

Mary M. Fanning, MD, PhD
Associate Director for Medical Affairs
Office of Generic Drugs

OCT 13 1993

NDA: 20-136
Amendment BC.
Torsemide tablets 5, 10, 20 and 100 mg.
Demadex[®].
Boehringer Mannheim.

Submission Date: May 25, 1993.

Reviewer: Patrick J Marroum.

Type of submission: Sponsor's request to amend dissolution specifications.

Background:

Torsemide is a new diuretic of the pyridine-sulfonylurea class. It is indicated for the treatment of hypertension. It is effective for the treatment of sodium and fluid retention due to congestive heart failure, renal disease or cirrhosis.

The specification of not less than — at 15 minutes in 900 ml of 0.1 N HCl using a USP type II apparatus at a paddle speed of 50 rpm were recommended by the FDA based on the biopharmaceutics review of the original NDA dated October 20, 1993. In the current submission, the sponsor is requesting to amend the above specification to not less than — in 30 minutes. The latter was originally proposed by the firm and considered inadequate by the Division of Biopharmaceutics. The firm's request is based on dissolution data obtained from validation

Results:

Table 1 to Table 4 shows the dissolution profiles obtained for the 5, 10, 20 and 100 mg tablets. The results show that for all strengths tested, the dissolution was very fast and complete by 15 minutes. All the batches tested passed the dissolution specification (even though, one of the batches required level 2 testing, it still met the dissolution specification).

RECOMMENDATION:

The dissolution results submitted by the sponsor do not support the request to amend the dissolution specifications set in the original NDA.

However, if the sponsor feels that this specification is inadequate, further data supporting their claim should be submitted for review. Note that this data should be obtained from the final market formulation specially with respect to _____

The Division of Biopharmaceutics, recommends that the dissolution specification for torsemide tablets not be amended from the original recommendation.

RD/FT initialed by A Parekh Ph.D.

LS

10/12/93

Patrick J Marroum Ph.D.

cc: NDA 20-136, HFD 110, HFD 426 (Fleischer, Marroum), Chron, Drug, FOI HFD 19.

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-110

CHEMISTRY REVIEW(S)

Office of Generic Drugs
Center of Drug Evaluation and Research
ABBREVIATED NEW DRUG APPLICATION
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO: No. 1

2. ANDA: 76-110

3. NAME AND ADDRESS OF APPLICANT:

TEVA Pharmaceuticals USA
Attn: Philip Erickson, R.Ph.
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090
215- 591-3141
FAX: 215- 591-8812

4. LEGAL BASIS for ANDA SUBMISSION:

The reference drug is Demadex[®] (NDA # 20-136) manufactured by Roche Laboratories Inc. The US patent #RE34672 expires August 11, 2006 without any protected exclusivity.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Torsemide Tablets, 5 mg, 10 mg,
20 mg and 100 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

TEVA Pharmaceuticals USA:
February 1, 2001 Submission of ANDA (received on 2/1/01)
February 23, 2001 Amendment
May, 2, 2001 Deficiency Letter Bioequivalence
May 16, 2001 Amendment

FDA:
03/05/01 Acknowledgment letter (including advice).

10. PHARMACOLOGICAL CATEGORY: Diuretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

See Item 37 for a complete list of DMFs.

Innovator: Roche NDA 20-136 (approved 08/23/93) Demadex®
(Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg).

13. DOSAGE FORM: Oral Tablets

14. Strength: 5 mg, 10 mg, 20 mg and 100 mg

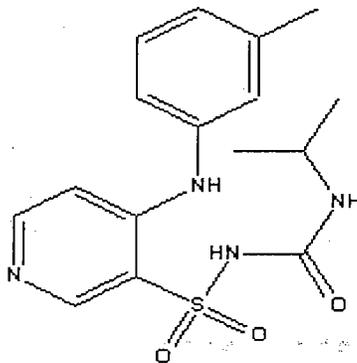
15. CHEMICAL NAMES AND STRUCTURE:

Generic name: Torsemide

Chemical name: 1-isopropyl-3-[(4-m-toluidino-3-pyridyl)
sulfonyl]urea

Formula: C₁₆H₂₀N₄O₃S Molecular Weight: 348.4

CAS registry number(s): 56211-40-6



16. RECORDS AND REPORTS: N/A

17. COMMENTS:

Both the bulk drug substance and the drug product do not have USP monographs.

DMF of the bulk drug substance was reviewed, and was found not adequate.

There are several CMC deficiencies in the ANDA. The estimated review time of TEVA Pharmaceuticals USA to these deficiencies will not exceed one hour.

Labeling review has been completed. Package Insert needs to be revised.

Bioequivalence review is adequate. The comments are subject to revision after the CMC, microbiology, labeling, or other scientific or regulatory issues.

EER is acceptable on March 6, 2001.

18. CONCLUSIONS AND RECOMMENDATIONS:

Not Approvable Minor

19. REVIEWER:

Roslyn F. Powers, Ph.D.

DATE COMPLETED:

June 6, 2001 (Revised:
6/13/01, 7/2/01, 7/17/01)

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Office of Generic Drugs
Center of Drug Evaluation and Research
ABBREVIATED NEW DRUG APPLICATION
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO: No. 2
2. ANDA: 76-110 (FIRST GENERIC)
3. NAME AND ADDRESS OF APPLICANT:

TEVA Pharmaceuticals USA
Attn: Philip Erickson, R.Ph.
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090
215- 591-3141
FAX: 215- 591-8812

4. LEGAL BASIS for ANDA SUBMISSION:

The reference drug is Demdex® (NDA # 20-136) manufactured by Roche Laboratories Inc. The US patent #RE34672 expires August 11, 2006 without any protected exclusivity.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

TEVA Pharmaceuticals USA:

February 1, 2001 Submission of ANDA (received on 2/1/01)

February 23, 2001 Amendment

May, 2, 2001 Deficiency Letter Bioequivalence

May 16, 2001 Amendment

September 4, 2001 Amendment

FDA:

03/05/01 Acknowledgment letter (including advice).

07/27/01 Deficiency Letter

10. PHARMACOLOGICAL CATEGORY: Diuretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

See Item 37 for a complete list of DMFs.

Innovator: Roche NDA 20-136 (approved 08/23/93) Demadex®
(Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg).

13. DOSAGE FORM: Oral Tablets

14. Strength: 5 mg, 10 mg, 20 mg and 100 mg

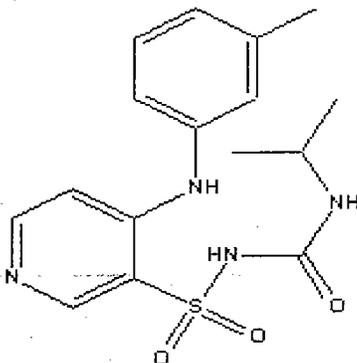
15. CHEMICAL NAMES AND STRUCTURE:

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: 348.4

CAS registry number(s): 56211-40-6



16. RECORDS AND REPORTS: N/A

17. COMMENTS:

Both the bulk drug substance and the drug product do not have USP monographs.

DMF of the bulk drug substance was reviewed, and was found not adequate.

Labeling review has been completed and labeling was found adequate 9/25/01.

Bioequivalence review is adequate.

EER is acceptable on March 6, 2001.

18. CONCLUSIONS AND RECOMMENDATIONS:

Not Approvable MINOR

19. REVIEWER:
Roslyn F. Powers, Ph.D.

DATE COMPLETED:
9/15/01 Revised: 10/30/01
11/27/01

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Office of Generic Drugs
Center of Drug Evaluation and Research
ABBREVIATED NEW DRUG APPLICATION
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO: No. 3
2. ANDA: 76-110 (FIRST GENERIC)
3. NAME AND ADDRESS OF APPLICANT:

TEVA Pharmaceuticals USA
Attn: Philip Erickson, R.Ph.
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090
215- 591-3141
FAX: 215- 591-8812

4. LEGAL BASIS for ANDA SUBMISSION:

The reference drug is Demadox® (NDA # 20-136) manufactured by Roche Laboratories Inc. The US patent #RE34672 expires August 11, 2006 without any protected exclusivity.

5. SUPPLEMENT(s): N/A
6. PROPRIETARY NAME: N/A
7. NONPROPRIETARY NAME: Torsemide Tablets, 5 mg, 10 mg,
20 mg and 100 mg
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:

TEVA Pharmaceuticals USA:

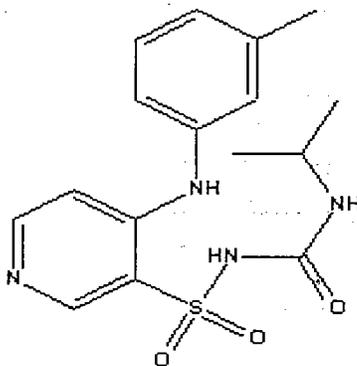
February 1, 2001	Submission of ANDA (received on 2/1/01)
February 23, 2001	Amendment
May 16, 2001	Amendment
September 4, 2001	Amendment
January 22, 2002	Amendment

FDA:

03/05/01	Acknowledgment letter (including advice).
05/02/01	Deficiency Letter Bioequivalence
07/27/01	Deficiency Letter
12/12/01	Deficiency Letter

10. PHARMACOLOGICAL CATEGORY: Diuretic

11. HOW DISPENSED: Rx
12. RELATED IND/NDA/DMF(s):
See Item 37 for a complete list of DMFs.
Innovator: Roche NDA 20-136 (approved 08/23/93) Demadex®
(Torseמידe Tablets, 5 mg, 10 mg, 20 mg and 100 mg).
13. DOSAGE FORM: Oral Tablets
14. Strength: 5 mg, 10 mg, 20 mg and 100 mg
15. CHEMICAL NAMES AND STRUCTURE:
Generic name: Torsemide
Chemical name: 1-isopropyl-3-[(4-m-toluidino-3-pyridyl)
sulfonyl]urea
Formula: C₁₆H₂₀N₄O₃S Molecular Weight: 348.4
CAS registry number(s): 56211-40-6



16. RECORDS AND REPORTS: N/A
17. COMMENTS:
Both the bulk drug substance and the drug product do not have USP monographs.
- DMF of the bulk drug substance was reviewed, and was found not adequate.
- Labeling review has been completed and labeling was found adequate.
- Bioequivalence review is adequate.
- EER is acceptable on March 6, 2001.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable MINOR Deficiency

19. REVIEWER: Roslyn F. Powers, Ph.D. DATE COMPLETED: 2/9/02
Revised: 3/25/02

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Office of Generic Drugs
Center of Drug Evaluation and Research
ABBREVIATED NEW DRUG APPLICATION
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO: No. 4

2. ANDA: 76-110 (FIRST GENERIC)

3. NAME AND ADDRESS OF APPLICANT:

TEVA Pharmaceuticals USA
Attn: Philip Erickson, R.Ph.
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090
215- 591-3141
FAX: 215- 591-8812

4. LEGAL BASIS for ANDA SUBMISSION:

The reference drug is Demadex® (NDA # 20-136) manufactured by Roche Laboratories Inc. The US patent #RE34672 expires August 11, 2006 without any protected exclusivity.

5. SUPPLEMENT (s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Torsemid Tablets, 5 mg, 10 mg,
20 mg and 100 mg

8. SUPPLEMENT (s) PROVIDE (s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

TEVA Pharmaceuticals USA:

February 1, 2001	Submission of ANDA (received on 2/1/01)
February 23, 2001	Amendment
May 16, 2001	Amendment
September 4, 2001	Amendment
January 22, 2002	Amendment
April 16, 2002	Amendment

FDA:

03/05/01	Acknowledgment letter (including advice).
05/02/01	Deficiency Letter Bioequivalence
07/27/01	Deficiency Letter
12/12/01	Deficiency Letter
4/5/02	Deficiency Letter

10. PHARMACOLOGICAL CATEGORY: Diuretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

See Item 37 for a complete list of DMFs.

Innovator: Roche NDA 20-136 (approved 08/23/93) Demadex®
(Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg).

13. DOSAGE FORM: Oral Tablets

14. Strength: 5 mg, 10 mg, 20 mg and 100 mg

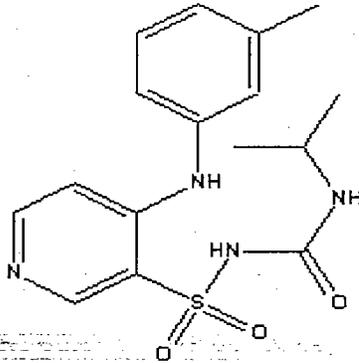
15. CHEMICAL NAMES AND STRUCTURE:

Generic name: Torsemide

Chemical name: 1-isopropyl-3-[(4-m-toluidino-3-pyridyl)
sulfonyl]urea

Formula: C₁₆H₂₀N₄O₃S Molecular Weight: 348.4 —

CAS registry number(s): 56211-40-6



16. RECORDS AND REPORTS: N/A

17. COMMENTS:

Both the bulk drug substance and the drug product do not have USP monographs.

DMF of the bulk drug substance was reviewed, and was found adequate.

Labeling review has been completed and labeling was found adequate.

Bioequivalence review is adequate.

EER is acceptable on March 6, 2001.

18. CONCLUSIONS AND RECOMMENDATIONS: Approvable

19. REVIEWER: Roslyn F. Powers, Ph.D. DATE COMPLETED: 26-APR-2002

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-110

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-110

APPLICANT: Teva Pharmaceuticals, USA

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

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

1. You have submitted a long term frozen stability study

[

]

2. Your dissolution testing method is different from that recommended by the Agency. Please submit dissolution testing results using the following FDA-recommended method:

Apparatus: 2 (paddle), 50 rpm
Medium: 0.1N HCl, 900 mL
Sampling Times: 10, 15, 30 and 45 minutes
No. of units to be tested: 12

Sincerely yours,

^

ISI

fn

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

Torsemide Tablets
5 mg, 10 mg and 20 mg
ANDA 76-110
Reviewer: Chandra S. Chaurasia

Teva Pharmaceuticals USA
North Wales, PA 19454
Submission Date:
02/01/2001

V:\firmsnz\Teva\ltrs&rev\76110sdw.201

Review of Two Bioequivalence Studies and Dissolution Data

Introduction

First Generic: Yes

Indication: Demadex[®] (Torsemide) is a loop diuretic of the pyridine sulfonylurea class. It is indicated for the treatment of hypertension and of edema associated with congestive heart failure.

Type of Submission: Original

Contents of Submission:

1. Fasting and non-fasting studies on the 20-mg tablet.
2. Dissolution data on 5-mg, 10-mg and 20-mg tablets. Waiver requests on the 5-mg and 10-mg strengths.

Reference Listed Drug: Demadex[®] (Torsemide) tablets are available in four strengths: 5 mg, 10 mg, 20 mg and 100 mg. The Orange Book (Electronic 2001) lists Demadex[®] 20-mg tablet manufactured by Roche Laboratories as the reference listed drug (NDA 20136, Aug. 23, 1993).

Note: Demadex[®] (torsemide) tablets 100 mg was first designated as the RLD. However, due to safety issue with the administration of 100 mg dose to normal volunteers, the Agency changed the RLD to Demadex[®] (Torsemide) Tablets, 20 mg (Attachment I, control documents OGD 01-003: Teva and OGD 00-532: _____)

Recommended Dose: The recommended initial dosage of Demadex[®] is 10-20 mg once daily for congestive heart failure. The dose may be titrated upward by approximately doubling until desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

Background

Pharmacokinetics and Metabolism: The bioavailability of Demadex[®] tablets is approximately 80%, with little intersubject variation. 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.

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 (Electronic PDR, 2001).

The following pharmacokinetic parameter values on Torsemide were obtained from NDA 20136 review dated February 28, 1991 (**Not to be released under FOI**):

Parameter	Oral 20-mg dose	Oral 40-mg dose
C_{max} (ng/mL)	2786	5023
T_{max} (hr)	0.98	0.92
AUCi (hr.ng/mL)	6622	12515
$T_{1/2}$ (hr)	3.67	3.15

Financial Disclosure: Form FDA 3454 was submitted. The firm certifies that it has not entered into any financial arrangement with clinical investigators and that its certification is in compliance with 21 CFR part 54 and 54.2(d) [Vol. 1.1, pp. 126].

Protocol No. 00318: A Randomized Two-way Crossover, Single-Dose, Bioequivalence Study of Teva Pharmaceuticals USA and Roche Laboratories Inc. Demadex® 20 mg Torsemide Tablets Administered as 2x20 mg Tablets in Healthy Adults Males and/or Females Under Fasting Conditions.

Study Information

Clinical Facility: _____
Principal Investigator: _____
Clinical Study Dates: Period I: December 06, 2000, Period II: December 13, 2000
Analytical Facility: _____
Analytical Section Head: _____
Analytical Study Dates: 12/22/00 to 01/12/01
Storage Period: 37 days

Treatment Information

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Torsemide	Demadex®
Manufacturer:	Teva Pharmaceuticals	Roche Laboratories

Manufacturing Date:	09/13/00	N/A
Expiration Date:	N/A	10/02
ANDA Batch Size:	—	N/A
Batch/Lot Number:	K-26696	0077
Potency:	97.8%	100.4%
Content Uniformity:	97.0% (RSD 0.9%)	98.1% (RSD 0.9%)
Strength:	20 mg	20 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	40 mg (2x20 mg)	40 mg (2x20 mg)
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	crossover
No. of Sequences:	2	Replicated Treatment	N
No. of Periods:	2	Balanced:	Y
No. of Treatments:	2	Washout Period:	7 days

Randomization: AB: 2,4,5,7,8,10,14,15,17,18,22,24,25
Scheme: BA: 1,3,6,9,11,12,13,16,19,20,21,23,26

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	26
Route of Administration:	Oral	No. of Subjects Completing:	24*
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	24
		No. of Subjects Statistical Analyses Performed:	24
Number of Doses:	N/A	No. of Dropouts:	Two*
Loading Dose:	N/A	Sex(es) Included:	Males and Females**
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	72

*Subject #4 female and subject #9, male were withdrawn from the study due to vomiting within the first 4 hours after drug administration in Period II.

**Eight females and 18 males.

Blood Sampling: One x 10 mL each before dosing (0-time) and at 0.25, 0.5, 0.667, 0.833, 1, 1.17, 1.33, 1.67, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours collected in vacutainers containing K3EDTA. The blood was centrifuged at 3000 rpm for 10 minutes at 4 °C, and all plasma samples were stored at -20 °C, pending assay.

Dietary Restrictions: No alcohol-, xanthine-, containing beverages/foods, grapefruit products for 48 hrs pre-dose and throughout sample collection period. No water 1 hr before/after dosing. Fasted overnight pre-dose and 4 hrs post-dose.

Activity Restrictions: Subjects remained ambulatory or seated upright for the first 4 hours post-dose, except when warranted by medical events. No strenuous activity during the housing period.

Drug Restrictions: No prescription drugs for a period of 14 days and OTC products 7 days preceding the study and throughout the study period. In the case of female subjects no oral contraceptives within 30 days prior to administration of the study medication. Restrictions related to method of contraception in female subjects are described in Vol. 2, pp. 968.

Study Results

1) Clinical

Adverse Events:

During the study, 74 adverse events were reported by 19 of the 26 subjects (Table C4, Vol. 1.3, pp. 1450). The adverse events are summarized in the table below:

Adverse Events	No of Adv. Events	Test/No. of sub.	Ref/No. of sub.	Severity	Resolution	Relationship to study drugs
Dizziness	28	4	10	Moderate	Spontaneous	Possibly/Probably
Headache	6	4	2	Mild	Spontaneous	Unrelated
Vomiting	6	1	3	Moderate	Spontaneous	Possibly
Nausea	8	2	2	Mild	Spontaneous	Unrelated
Hot Flushes	6	3	2	Moderate	Spontaneous	Probably
Sore Throat	3	1	2	Mild	Spontaneous	Unrelated
Stomach Cramp	1	1		Mild	Spontaneous	Possibly
Fainting	3	1	2	Moderate	Spontaneous	Possibly
Increased Urinary Frequency	4	1	3	Mild	Spontaneous	Possibly
Feels Hungry	1	1		Mild	Spontaneous	Unrelated
Protein in urine (0.3 g/L)	1	1		N/A	Spontaneous	Unlikely
Glucose AC (9.0 mmol/L)	1		1	N/A	Unresolved*	Unlikely
Bruise on left knee	1		1	Mild	Spontaneous	Unrelated
Bruise on right knee	1		1	Mild	Spontaneous	Unrelated
Back Pain	1		1	Mild	Spontaneous	Possibly
Redness on the left ankle	1	1		Mild	With Treat	Unrelated
Swollen left ankle	1	1		Mild	With Treat	Unrelated
Pain left ankle	1	1		Mild	With Treat	Unrelated

Analytical

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3) Pharmacokinetic and Statistical Analysis:

Mean Plasma Concentrations: Table 1 and Figure 1

Pharmacokinetics Measures: Tables 2 and 3

Table 1. Fasting Single-Dose In Vivo Bioequivalence Study # 00318 Arithmetic Mean Plasma Torsemide Concentrations [ng/mL]* (\pm S.D.) Vs. Time (N = 24)

Time	Test (treat A)		Ref (treat B)		A/B
	Conc.	S.D.	Conc.	S.D.	
0.0	0.00	-	0.00	-	-
0.25	1589.25	1362.34	917.69	914.45	1.73
0.50	4885.00	2065.0	4330.35	1840.18	1.13
0.67	5700.83	1985.27	5201.25	1848.70	1.10
0.83	5554.38	1863.16	5234.00	1629.91	1.06
1.0	4927.08	1400.39	4947.50	1795.94	1.00
1.17	4355.83	1201.63	4537.08	1478.10	0.96
1.33	4004.17	1243.02	4056.25	1093.80	0.99
1.67	3028.75	1012.78	3128.75	932.77	0.97
2.0	2340.42	851.60	2331.25	678.95	1.00
3.0	1466.08	630.21	1480.54	577.22	0.99
4.0	933.21	373.32	964.33	420.78	0.97
6.0	444.46	207.47	486.67	304.30	0.91
8.0	274.29	116.82	299.75	158.0	0.92
10	175.72	88.64	189.54	109.16	0.93
12	119.14	59.54	130.97	66.39	0.91
16	59.71	27.20	63.05	31.76	0.95
24	17.50	12.53	19.12	12.76	0.92

*All of the torsemide plasma samples between 0.5 to 2.0 hours were pre-diluted and analyzed with three diluted high QC samples for each run.

Table 2. Fasting Single-Dose In Vivo Bioequivalence Study # 00318 Arithmetic Means (\pm SD) of Pharmacokinetic Parameters for Torsemide (N = 24)

PK Measures	Test (A)	Reference (B)
AUCt [ng•hr/mL]	13849.67 \pm 3975.99	13719.46 \pm 3578.96
AUCi [ng•hr/mL]	14000.63 \pm 4008.45	13891.13 \pm 3598.21
Cmax [ng/mL]	6330.42 \pm 1806.84	5948.33 \pm 1618.33
tmax [hr]	0.77 \pm 0.29	0.93 \pm 0.50
k _{el} [1/hr]	0.1613 \pm 0.0334	0.1588 \pm 0.0333
t _{1/2} [hr]	4.45 \pm 0.78	4.55 \pm 0.93

Table 3. Summary Statistics for Torsemide Single-Dose In Vivo Bioequivalence Study # 00318 Under Fasting Conditions, N = 24

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (ng•hr/mL)	13365.50	13274.74	0.07089	1.01	97.2-104.3
Ln AUCi (ng•hr/mL)	13553.84	13445.03	0.07146	1.01	97.0-104.1
Ln Cmax (ng/mL)	6117.26	5721.57	0.19416	1.07	97.1-117.7

*geometric mean values for ln-transformed data reported

Reassays:

No repeat assay due to any pharmacokinetic anomaly has been reported in this study. A total of 53 out of 862 (6.1%) samples were repeated due to analytical reasons as described below:

Analytical Reasons	No of samples repeated (% of total samples)
Values above the limit of quantitation	34 (3.9%)
Upper limit of quantitation eliminated	4
Unknown processing error	10 (1.16%)
Peak in the zero hour of sample without internal standard	3
Peak in the zero hour	1
Laboratory accident	1

Comments: On pharmacokinetic data

1. The pharmacokinetic measures (AUC_t , AUC_i , C_{max} , t_{max} and $t_{1/2}$) and confidence intervals of AUC_t , AUC_i and C_{max} for torsemide as calculated by the reviewer were in agreement with the values reported by the firm.
2. There were no statistically significant period effects for any of these PK measures.
3. The 90% confidence intervals for torsemide of In-transformed AUC_t , AUC_i , and C_{max} ratios are within the acceptable limits of 80-125%.
4. Since the subjects who completed the study include 8 females and 18 males, the reviewer analyzed statistical data for any gender effect. No significant difference between treatment and gender was observed for In- AUC_t , In- AUC_i and In- C_{max} for torsemide (data not shown in the review).

Protocol No. 00319: A Randomized Three-way Crossover, Single-Dose, Bioequivalence Study of Teva Pharmaceuticals USA and Roche Laboratories Inc. Demadex® 20 mg Torsemide Tablets Administered as 2x20 mg Tablets in Healthy Adults Males and/or Females Under Fasting and Non-fasting Conditions.

Study Information

Clinical Facility: _____

Principal Investigator: _____

Clinical Study Dates: Group I

Period I: 12/04/00, Period II: 12/14/00 and, Period III: 12/21/00

Group II

Period I: 12/14/00, Period II: 12/21/00 and Period III: 01/04/01

Note: The firm's original protocol included 18 healthy adult males and/or females, non-smoking subjects for this study. The firm amended protocol states, "considering that 17 subjects were dosed in the first period of the study and only 14 subjects confirmed their participation to the second period, an add-on study will be performed with 12

subjects. Therefore, a total of 29 subjects will be dosed in order to have 18 subjects completing the study."

Analytical Facility: _____
Analytical Section Head: _____
Analytical Study Dates: 01/09/01 to 01/26/01
Storage Period: 54 days

Treatment Information

Treatment ID:	A	B	C
Test or Reference	T	R	T
Product Name:	Torsemide	Demadex	Torsemide
Manufacturer:	Teva	Roche	Teva
Batch Number:	K-26696	0077	K-26696
Dose Administered	40 mg (2x20 mg)	40 mg (2x20 mg)	40 mg (2x20 mg)
Study Condition:	fed	fed	fasting
Length of Fasting:	overnight	overnight	overnight
Standardized	Y	Y	N
Breakfast*:			

*Standardized Breakfast consisted of the following diet:

- Buttered English muffin 1
- Fried egg 1
- American cheese slice 1
- Bacon strips 2
- Hash brown potatoes 1 serving
- Whole milk 240 mL
- Orange juice 180 mL

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	Crossover
No. of Sequences:	6	Replicated Treatment	N
No. of Periods:	3	Balanced:	N
No. of Treatments:	3	Washout Period:	7 days

Randomization Scheme:

Group I (Vol. 6, pp. 3529)

- ABC: 1,2,15
- ACB: 5,10,16
- BAC: 6,8,13
- BCA: 3*, 9,18
- CAB: 4,12,17
- CBA: 7,11,14

Group II (Add-on, Vol. 6, pp. 3531)

- ABC: 20,26
- ACB: 22,29
- BAC: 23,27
- BCA: 3*, 25
- CAB: 19,28
- CBA: 21,24

*The firm notes that since #3 was originally not assigned to a volunteer, the randomization code for this subject was retranscribed in Group II from the original randomization of Group I.

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	29
Route of Administration:	Oral	No. of Subjects Completing:	23*
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	23*
Number of Doses:	N/A	No. of Dropouts:	Six*
Loading Dose:	N/A	Sex(es) Included:	Males and Females**
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	130

*Subject #4 and 12 elected to withdraw from the study prior to Period 2 (Test fed), due to a personal reason.

Subject #5 elected to withdraw from the study prior to drug administration in Period 2 (Test fasted) due to a personal reason.

Subject #14 elected to withdraw from the study prior to Period 3 (Test fed)

Subject #16 was withdrawn by the Principal Investigator, prior to Period 2 (Test fasted) due a medical condition.

Subject #29 was withdrawn from the study after the 4.0-hour post-dose blood draw in Period 3 (Ref fed), due to vomiting.

**Twelve females and 17 males

Dietary Restrictions:
Activity Restrictions:
Drug Restrictions: } same as those reported in the fasting study*

Blood Sampling: One x 10 mL each before dosing (0-time) and at 0.25, 0.5, 0.667, 0.833, 1, 1.17, 1.33, 1.67, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours collected in vacutainers containing K3EDTA. The blood was centrifuged at 3000 rpm for 10 minutes at 4 °C, and all plasma samples were stored at -20 °C, pending assay.

Study Results

1) Clinical

During the study, 130 adverse events were reported — 59: test non-fasting, 36 reference non-fasting, and test fasting: 35 (Table C4, Vol. 1.6, pp. 3372). The adverse events are summarized in the table below.

Adverse Events	No of Adv. Events	Test Fed/ No. of sub.	Ref Fed/ No. of sub.	Test Fast/ No. of sub	Severity	Resolution	Relationship to study drugs
Dizziness	25	6	4	8	Mild/Moderate	Spontaneous	Possibly/Probably
Headache	18	8	1	4	Mild	Treatment (acetaminophen 2x325 mg)	Possibly
Vomiting	1	1	-	-	Moderate	Spontaneous	Unlikely
Vomiting	1	-	1	-	Severe	Spontaneous	Possibly
Nausea	13	5	2	3	Mild/Moderate	Spontaneous	Possibly/Probably
Hot Flushes	11	2	4	2	Mild/Moderate	Spontaneous	Possibly/Probably

Sore Throat	2	1	-	1	Mild	Unresolved	Unlikely
Abdominal Cramp	2	1	1	-	Mild	Spontaneous	Unlikely
Leg and/or Body Cramp	9	1	-	1	Mild	Spontaneous	Unrelated
Fainting	7	1	1	1	Moderate/Severe	Spontaneous	Possibly/Probably
Increased Urinary Frequency	8	3	1	3	Mild	Spontaneous	Possibly/Probably
Shortness in Breathing	2	1	-	1	Mild	Spontaneous	Possibly
Numbness in Arms	2	1	1	-	Moderate	Spontaneous	Unlikely
Numbness in Legs	1	1	-	-	Moderate	Spontaneous	Unlikely
Muscular Pain	1	1	-	-	Mild	Spontaneous	Unlikely
Heavy Head	1	-	-	1	Mild	Spontaneous	Probably
Shivering	1	1	-	-	Mild	Treatment/acetaminophen 1x500 mg	Unrelated
Feverish	1	1	-	-	Mild	Spontaneous	Probably
Nasal Congestion	2	1	1	-	Mild	Spontaneous	Unrelated
Runny Nose	1	-	1	-	Mild	Spontaneous	Unrelated
Coughing	1	1	-	-			
Drowsiness	1	-	1	-	Mild	Spontaneous	Unlikely
Dry Throat	1	-	1	-	Mild	With Treatment/acetaminophen 2x325 mg	Unrelated
Sweating	1	1	-	-	Mild	Spontaneous	Unlikely
Difficulty in Bowel Movement	2	1	-	1	Mild/Moderate	Treatment/Glycerin Suppository	Possibly
Swelling of the hand	1	1	-	-	Mild	Spontaneous	Unlikely
Weakness	2	1	1	-	Moderate	Spontaneous	Possibly
Heavy on the leg	2	-	1	-	Mild	Spontaneous	Probably
Fatigue/Tired	6	1	1	2	Mild/Moderate	Spontaneous	Possibly/Probably
Loose Stool	1	-	1	-	Mild	Spontaneous	Possibly
Coughing	1	1	-	-	Mild	Onset 2-days post-dose, Treatment/Fludivial (active ingredients not known)	Unrelated
High creatinine (143 umol/L)	1	1	-	-	N/A	Spontaneous	Unlikely
Protein in urine (0.3 g/L)	1	-	1	-	N/A	Pending	Pending

Safety Monitoring: Same as described in the fasting study.

Protocol Deviations: None other than minor sampling deviations.

2) **Analytical:** Same method as that used in the fasting study. Within study day assay validations are given below:

[]

Comments on Analytical Methodology:

[]

3) **Pharmacokinetic and Statistical Analysis:**

The sponsor performed ANOVA on the pharmacokinetic measures based on the model $Y = \text{gr seq seq*gr sub (seq*gr) per (gr) trt (Vol. 5; pp. 2859)}$

This reviewer reanalyzed the data using the following statistical models:

Model 1: $Y = \text{gr seq seq*gr sub(seq*gr) per(gr) trt trt*gr}$

Model 2: $Y = \text{gr seq seq*gr sub(seq*gr) per(gr) trt}$

Model 3: $y = \text{seq sub(seq) per trt}$

Pharmacokinetic measures based on these models are summarized in Table 4.

None of the three models detected any statistically significant difference between treatments for $\ln\text{-AUC}_t$, $\ln\text{-AUC}_i$ and $\ln\text{-C}_{max}$, for torsemide. All ratios for \ln -transformed geometric means of AUC_t , AUC_i and C_{max} were within the acceptable range of 80 to 125% for torsemide.

Table 4. Results on torsemide from three different statistical models

BE Measures	Model 1 T/R, WSV*	Model 2 T/R, WSV	Model 3 T/R, WSV
AUC_t	0.95, 7.54%	0.95, 7.54%	0.96, 8.05%
AUC_i	0.95, 7.49%	0.95, 7.51%	0.96, 7.97%
C_{max}	0.92, 19.54%	0.91, 21.03%	0.92, 21.52%

WSV= within subjects variation

Mean Plasma Concentrations of the test and reference treatments and pharmacokinetic measures are summarized in Tables 5 and 6, respectively. The plasma-concentration time plot is given in Figure 2.

Table 5. Fasting/Non-fasting Single-Dose In Vivo Bioequivalence Study # 00319 Arithmetic Mean Plasma Torsemide Concentrations [ng/mL]* (\pm S.D.) Vs. Time (N = 23)

Time (hr)	Test (Non-fasting) A		Ref (Non-fasting) B		Test (Fasting) C		(A/B)	(A/C)
	Mean	SD	Mean	SD	Mean	SD		
0.0	0.00	-	0.00	-	0.00	-	-	-
0.25	261.97	472.83	237.37	451.13	1580.77	1284.55	1.10	0.17
0.50	1216.51	1359.14	1085.62	1666.61	5759.57	2859.25	1.12	0.21
0.67	1826.67	1666.79	1731.22	2046.15	6206.96	2784.43	1.06	0.29
0.83	2391.84	1916.06	2304.66	2293.82	6102.17	2278.16	1.04	0.39
1.0	2572.39	1681.33	2677.45	2209.23	5535.65	1714.82	0.96	0.46
1.17	2893.96	1590.28	2959.70	2018.30	4997.83	1481.85	0.98	0.58
1.33	3206.95	1454.92	3123.91	1924.20	4345.22	1405.52	1.03	0.74
1.67	3225.65	1250.48	3536.52	1608.88	3427.39	1141.66	0.91	0.94
2.0	3075.17	976.81	3415.44	1274.64	2731.74	961.30	0.90	1.13
3.0	2893.04	956.42	2865.22	878.94	1786.48	706.51	1.01	1.62
4.0	1883.91	820.72	2118.35	1141.59	1165.96	479.78	0.89	1.62
6.0	853.65	377.56	810.17	392.58	553.65	207.93	1.05	1.54
8.0	500.30	211.57	501.00	272.52	376.13	164.25	1.00	1.33
10	295.22	148.83	321.39	164.06	234.74	134.04	0.92	1.26
12	182.37	84.39	190.57	108.59	162.68	91.64	0.96	1.12
16	88.65	48.79	95.85	62.99	81.14	57.75	0.92	1.09
24	25.20	18.39	31.25	24.43	25.21	21.10	0.81	1.00

*For all of the torsemide plasma-concentrations exhibiting a value of more than 4000 ng/mL, samples were reanalyzed by dilution.

Table 6. Fasting/Non-fasting Single-Dose In Vivo Bioequivalence Study # 00319 Arithmetic Means (\pm SD) of Pharmacokinetic Parameters for Torsemide, N = 23

PK Measures	Test (Non-fasting) A	Ref (Non-fasting) B	Test (Fasting) C
AUC _t (ng·hr/mL)	16043.78 \pm 3662.61	16704.57 \pm 3777.94	16373.35 \pm 4778.73
AUC _i (ng·hr/mL)	16232.30 \pm 3745.65	16923.17 \pm 3885.45	16575.26 \pm 4863.79
C _{max} (ng/mL)	4422.61 \pm 844.53	4859.57 \pm 489.39	7336.52 \pm 2250.32
t _{max} (hr)	1.91 \pm 0.92	1.95 \pm 0.95	0.90 \pm 0.52
Kel	0.1735 \pm 0.0385	0.1693 \pm 0.0409	0.1660 \pm 0.0315
t _{1/2} (hr)	4.19 \pm 0.96	4.33 \pm 1.08	4.29 \pm 0.65

Table 7. Summary Statistics for Torsemide Single-Dose In Vivo Bioequivalence Study # 00319 Under Fasting/Non-fasting Conditions (N=23)

PK Measures*	Geometric Mean			Root Mean Square	Ratio	
	TREAT A	TREAT B	TREAT C		A/B	A/C
Ln AUC _t (ng·hr/mL)	15686.08	16445.00	15594.56	0.07548	0.95	1.00
Ln AUC (ng·hr/mL)	15835.56	16651.21	15781.14	0.07488	0.95	1.00
Ln C _{max} (ng/mL)	4384.12	4756.67	6840.56	0.19537	0.92	0.64

*geometric mean values for ln-transformed data reported

Reassays:

No repeat assay due to any pharmacokinetic anomaly has been reported in this study. A total of 33 out of 1241 (2.7%) samples were repeated due to analytical reasons as described below:

Analytical Reasons	No of samples repeated (% of total samples)
Values above the limit of quantitation	16 (1.29%)
Unacceptable chromatography	3
Unknown processing error	7 (0.56%)
Peaks at the zero-hour without internal standard	3
Retention time shift	2
Low internal standard response	1
Laboratory accident	1

Comments: On pharmacokinetic/statistical data:

1. The pharmacokinetic measures (AUC_t , AUC_i , and C_{max}) and ratios of their ln-transformed means for torsemide were recalculated by the reviewer. The reported values are in agreement with those obtained by the reviewer. There were no statistically significant period effects for any of these measures.
2. Ratios of ln-transformed geometric means for AUC_t , AUC_i , and C_{max} of torsemide between test non-fasting and reference non-fasting are within the acceptable limits of 0.80-1.25.
3. For the test product the mean C_{max} value was reduced by 36% and the mean t_{max} value was increased by one hour (1.91 hr non-fasting vs. 0.9 hr fasted) under non-fasting conditions.

Formulation (Not to be released under FOI)

Comparative Components and Composition Table

	Amount: mg/tablet		
	5-mg Strength	10-mg Strength	20-mg Strength
Torsemide	5.0	10.0	20.0
Lactose Anhydrous NF			
Crospovidone, NF			
Povidone, USP			
Microcrystalline Cellulose NF			
Magnesium Stearate, NF			
Total Weight	100.0	200.0	400.0

Comments on Formulation: (Not to be released under FOI)

1. The formulation for the 5-mg and 10-mg torsemide tablets are proportionally similar to that of the 20-mg strength per definition 1 in BA/BE Guidance for Industry for Orally Administered Drug Products issued on October 27, 2000.

2. All inactive ingredients utilized in the formulation are within the listed levels in the Inactive Ingredient Guide (1996) for oral tablets.

Dissolution

At present there is no USP dissolution method for torsemide tablets. The firm has used the following in-house dissolution method:

Apparatus: 2 (paddle), 50 rpm

Medium: _____

Sampling Times: 15, 30, 45 and 60 minutes

Tolerance (firm's proposed): NLT _____ (Q) in 30 minutes

Number of tablets: 12

The dissolution results are summarized in the following Table:

Test Products: Torsemide Tablets Dose strengths: 5, 10 and 20 mg Reference Products: Demadex® Tablets, 5, 10 and 20 mg Assay methodology: _____						
Results of dissolution testing Percentage dissolved in minutes						
Sampling time (min)	Test product Torsemide Tablets 5 mg, Lot # K26694			Reference Product Demadex® Tablets 5 mg, Lot # 0005-50, Exp. 10/02		
	Mean	Range	%CV	Mean	Range	%CV
15	98	_____	2.0	99	_____	3.5
30	99	_____	1.6	101	_____	2.8
45	99	_____	1.5	100	_____	2.8
60	100	_____	0.9	100	_____	3.0
Sampling time (min)	Test product Torsemide Tablets 10 mg, Lot # K26695			Reference Product Demadex® Tablets 10 mg, Lot # 0012 Exp. 10/02		
	Mean	Range	%CV	Mean	Range	%CV
15	95	_____	1.0	96	_____	2.4
30	96	_____	0.9	97	_____	2.4
45	97	_____	1.0	97	_____	2.3
60	97	_____	1.2	97	_____	2.4
Sampling time (min)	Test product Torsemide Tablets 20 mg, Lot # K26696			Reference Product Demadex® Tablets 20 mg, Lot # 0077 Exp. 10/02		
	Mean	Range	%CV	Mean	Range	%CV
15	96	_____	1.8	94	_____	4.6
30	98	_____	0.9	99	_____	1.2
45	98	_____	1.1	99	_____	1.3
60	98	_____	1.1	99	_____	1.1

Comments on Dissolution Testing:

1. The test and reference products used in the dissolution testing were from the same

lots used in the *in vivo* bioequivalence studies.

2. In the original application of the RLD (NDA 20-136), the innovator had submitted dissolution testing data using a USP type II apparatus in _____ at a speed of 50 rpm, with a dissolution specification of _____ at 30 minutes, sampling times at 10, 20, 30 and 40 minutes (Submission Date: April 16, 1992; Review Date: October 20, 1992). However, the Agency considered the dissolution incomplete, and requested the sponsor to conduct dissolution in 0.1N HCl and simulated intestinal fluids without enzymes (phosphate buffer pH 7.4).
3. Upon reviewing subsequent submission on dissolution testing of the RLD (Submission Date: May 25, 1991, Review Date: October 12, 1993), the Agency recommended the following dissolution method for torsemide tablets (Attachment II):

Apparatus: 2 (paddle), 50 rpm
Medium: 0.1N HCl, 900 mL
Tolerance: NLT _____ (Q) in 15 minutes

4. Since the firm's dissolution method uses water instead of 0.1N HCl as recommended in the FDA method, the firm's dissolution is not acceptable.

Deficiencies:

1. The firm has submitted a long-term frozen stability study covering a period of 46 days. However, the overall storage period for the plasma torsemide samples in the non-fasting study is 54 days. Analytical method validation for torsemide for the assay of plasma samples under non-fasting conditions is incomplete, and hence the non-fasting biostudy is incomplete.
2. The firm's dissolution method is different from that recommended by the Agency, and is not acceptable. The firm is advised to use the following method:

Apparatus: 2 (paddle), 50 rpm
Medium: 0.1N HCl, 900 mL
No. of units to be tested: 12
Sampling Times: 10, 20, 30 and 40 minutes

Recommendations

1. The single-dose fasting bioequivalence study conducted by Teva Pharmaceuticals on its Torsemide 20-mg Tablet, Lot # K26696, comparing it to Demadex® 20-mg Tablet, Lot #0077 has been found acceptable. However, the single-dose non-fasting study conducted by the firm on its Torsemide 20-mg Tablet, Lot # K26696, comparing it to Demadex® 20-mg Tablet, Lot #0077 has been found incomplete by the Division of Bioequivalence due to the deficiency in the long term frozen

the Division of Bioequivalence due to the deficiency in the long term frozen stability.

2. The dissolution testing conducted by the firm on its Torsemide 20-mg, 10-mg and 5-mg tablets is not acceptable. The firm is advised to conduct dissolution testing using the following FDA-recommended method:

Apparatus: 2 (paddle), 50 rpm
Medium: 0.1N HCl, 900 mL
Sampling Times: 10,15, 30 and 45 minutes
No. of units to be tested: 12

The firm should be informed of the above recommendations.

/S/
Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 4/6/2001

RD INITIALED YHUANG
FT INITIALED YHUANG

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y

Date: 4/6/2001

fw Concur:
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: 4/27/2001

ANDA: 76-110

APPLICANT: Teva Pharmaceuticals, USA

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

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CC: DIVISION FILE, HFD-652/Bio Secretary-Bio Drug File, HFD-650/C.Chaurasia

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-110
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)
HFD-652/CS Chaurasia
HFD-652/YC Huang
HFD-617/K Scardina
HFD-650/Dale Conner

4/6/2001

W H 4/6/2001
4/27/2001

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Printed in Final on 04/06/2001

BIOEQUIVALENCY – **Incomplete**

Submission Dates:02/01/2001

- | | | |
|----|-------------------------------------|-------------------------|
| 1. | FASTING STUDY (STF) o/c | Strength: 20 mg |
| | <hr/> | Outcome: AC |
| 2. | FOOD STUDY (STP) o/c | Strength: 20 mg |
| | <hr/> | Outcome: IC |
| 3. | DISSOLUTION WAIVER (DIW) o/c | Strengths: 10 mg |
| | | Outcome: IC |
| 4. | DISSOLUTION WAIVER (DIW) o/c | Strengths: 5 mg |
| | | Outcome: IC |

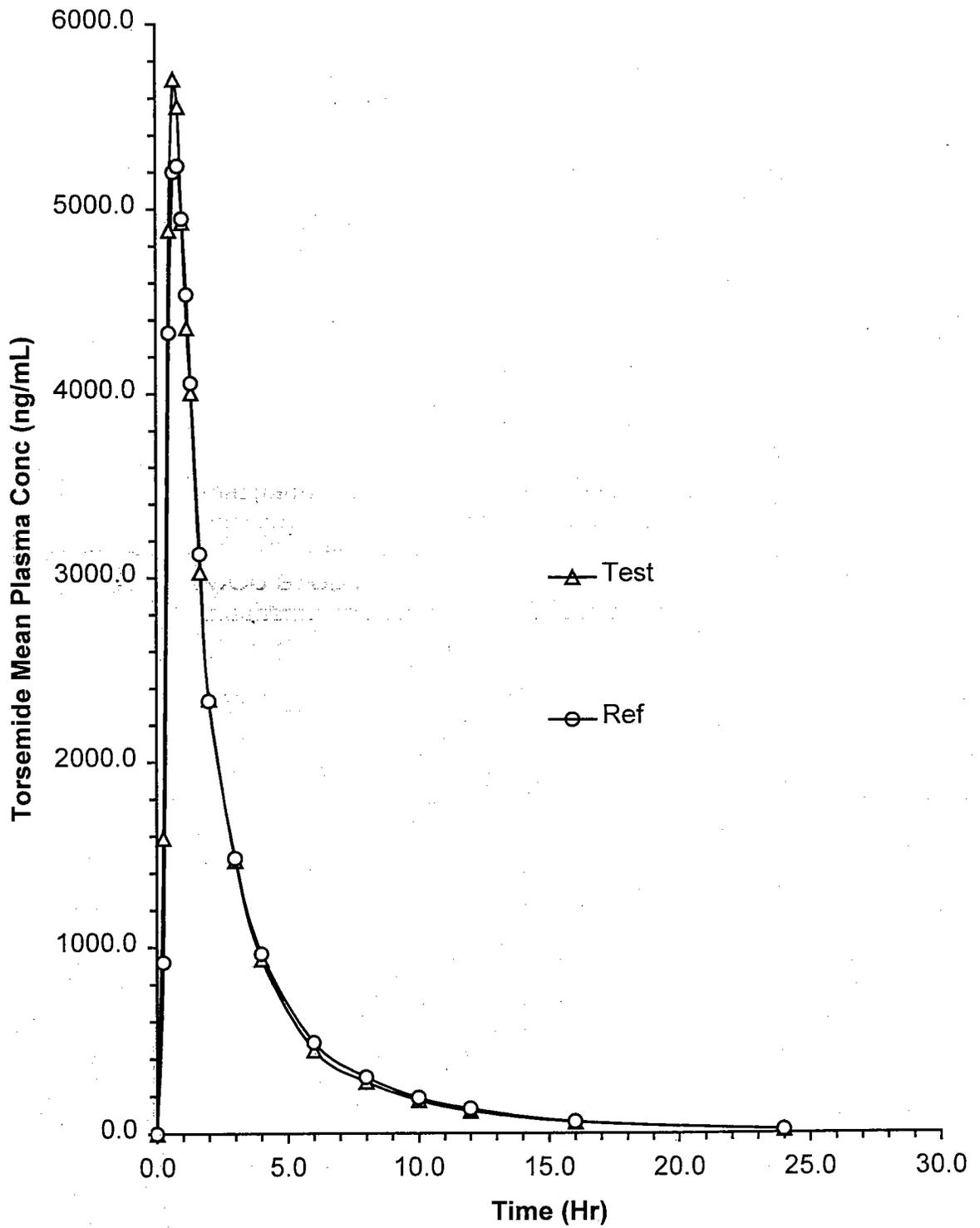
Outcome Decisions:

IC - Incomplete

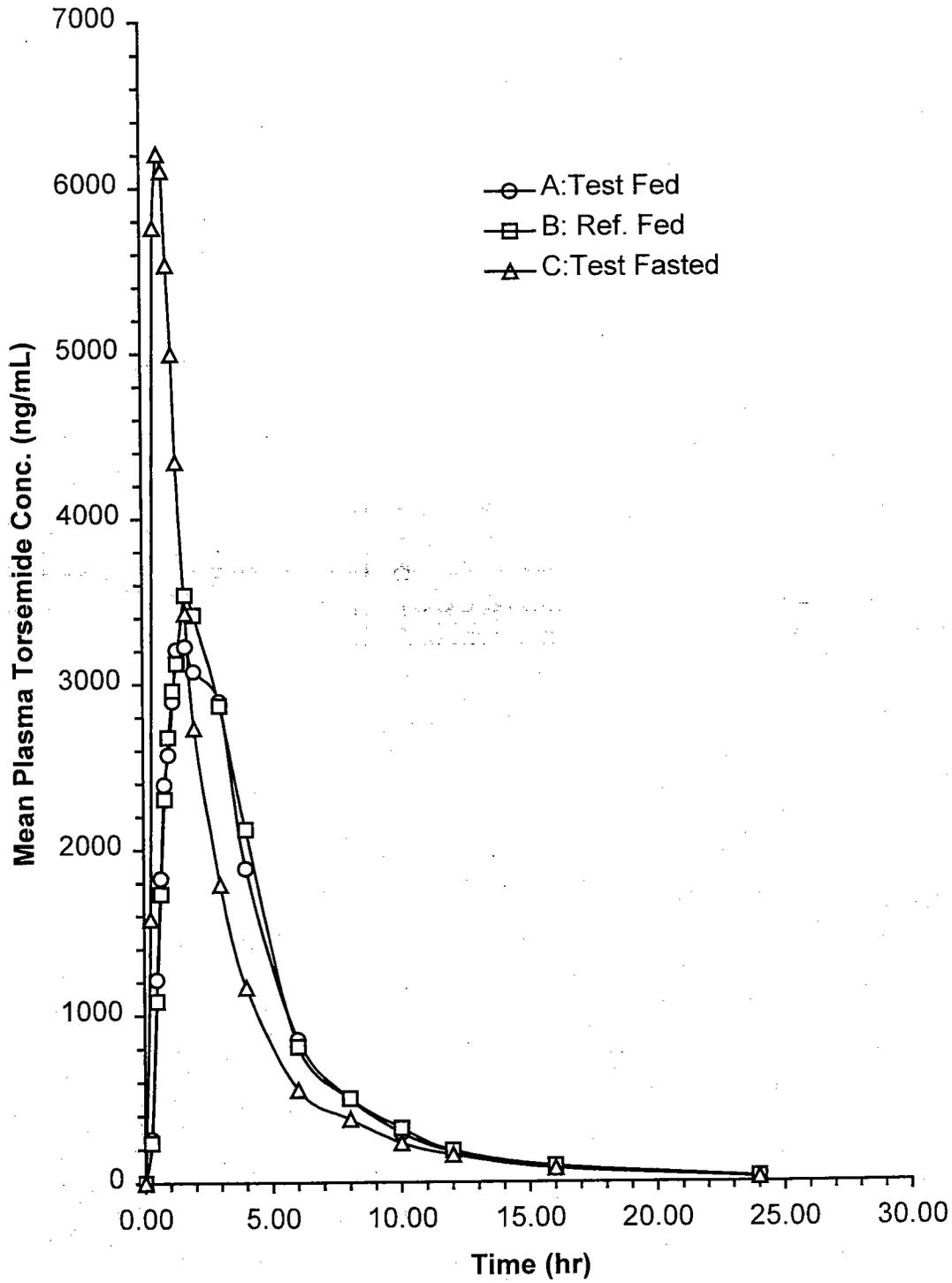
WinBio Comments:

- Fasting study on Torsemide Tablets, 20 mg is acceptable.
- Non-fasting study on Torsemide Tablets, 20 mg, is incomplete.
- Biowaiver requests on Torsemide Tablets, 10 mg and 5 mg are not granted.

**Fig.1. ANDA 76-110 Torsemide Plasma-Concentration
Time Plot (Fasting Study, N=24)**



**Fig. 2. ANDA 76-110: Torsemide Plasma-Concentration
Time Plot: Non-Fasting Study (N=23)**



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-110

APPLICANT: Teva Pharmaceuticals, USA

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

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

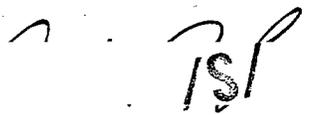
We acknowledge that the following dissolution testing has been incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37 °C using USP apparatus 2 (paddle) at 50 rpm. The test products should meet the following interim specifications:

Not less than (Q) of the labeled amount of torsemide in the dosage form is dissolved in 15 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,


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

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AJM

2.1

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA #: 76-110

SPONSOR: Teva Pharmaceuticals, USA

DRUG AND DOSAGE FORM: **Torsemid Tablets**

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

TYPES OF STUDIES: Fasting and non-fasting Bioequivalence Studies on 20-mg strength.

CLINICAL STUDY SITE (S): _____

ANALYTICAL SITE (S): _____

STUDY SUMMARY : Bioequivalence studies are acceptable.

DISSOLUTION: Dissolution testing on 5 mg, 10 mg, 20 mg and 100 mg strengths is acceptable

DSI INSPECTION STATUS

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

PRIMARY REVIEWER: CS CHANDRA S. CHAURASIA, Ph. D. BRANCH : I

INITIAL : CS DATE : 5/25/2001

TEAM LEADER : YH YIH-CHAIN HUANG, Ph. D. BRANCH : I

INITIAL : YH DATE : 5/25/2001

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

INITIAL : DP DATE : 6/26/01

Torsemide Tablets
5 mg, 10 mg, 20 mg and 100 mg
ANDA 76-110
Reviewer: Chandra S. Chaurasia

Teva Pharmaceuticals USA
North Wales, PA 19454
Submission Dates:
~~02/23/2001~~
05/16/2001

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Review of A Bioequivalence Study Amendment and Waiver Request on Higher Strength (100 mg)

OBJECTIVE

Review of Teva Pharmaceuticals' amendment responding to the Agency's letter dated May 02, 2001, and waiver request on the higher 100-mg strength.

CONTENTS OF SUBMISSION

1. Long term frozen stability data (5/2/01)
2. Dissolution data on 5-mg, 10-mg, 20-mg and 100-mg strengths (5/2/01).
3. New Waiver Request on the 100-mg tablets (2/23/01).

Reference Listed Drug: Demadex[®] (Torsemide) tablets are available in four strengths: 5 mg, 10 mg, 20 mg and 100 mg. The Orange Book (Electronic 2001) lists Demadex[®] 20-mg tablet manufactured by Roche Laboratories as the reference listed drug (NDA 20136, Aug. 23, 1993).

Note: Demadex[®] (torsemide) tablets 100 mg was first designated as the RLD. However, due to safety issue with the administration of 100 mg dose to normal volunteers, the Agency changed the RLD to Demadex[®] (Torsemide) Tablets, 20 mg (control documents OGD 01-003: Teva and OGD 00-532: ~~_____~~)

BACKGROUND

Teva Pharmaceuticals previously submitted single-dose bioequivalence studies under fasting and non-fasting conditions comparing its Torsemide, 20 mg, Tablet, Lot # K26696, to Demadex[®] 20-mg Tablet, Lot #0077 (manufactured by Roche Laboratories; Submission Date: December 12, 2000; Review Date: April 27, 2001)

[]

In addition, the dissolution testing method used by the firm in the original application was found deficient. The firm was advised to use the following method:

Apparatus: 2 (paddle), 50 rpm
Medium: 0.1N HCl, 900 mL
Sampling Times: 10, 15, 30 and 45 minutes
No. of units to be tested: 12

In the current submission, the firm has responded to the above deficiencies.

REVIEW OF THE FIRM'S RESPONSE

Deficiency 1:

[]

Firm's Response:

[]

Comments on Analytical Methodology:

The analytical method validation for torsemide is acceptable.

Deficiency 2: *Your dissolution testing method is different from that recommended by the Agency. Please submit dissolution testing results using the following FDA-recommended method:*

Apparatus: 2 (paddle), 50 rpm
Medium: 0.1N HCl, 900 mL
Sampling Times: 10, 15, 30 and 45 minutes
No. of units to be tested: 12

Firm's Response:

The firm has provided comparative dissolution testing results on torsemide tablets 5-mg, 10-mg and 20-mg using the Agency's recommended method. The dissolution results are given in the table below:

Test Products: Torsemide Tablets Dose strengths: 5, 10 and 20 mg Reference Products: Demadex® Tablets, 5, 10 and 20 mg Apparatus 2 (paddle), 50 rpm Medium: 0.1N HCl, 900 mL Assay methodology: _____						
Site of Dissolution Testing: Teva Pharmaceutical Industries Ltd. Pharmaceutical Operations Division – Research and Development KFAR SABA, ISRAEL Analysis Date: May 2001						
Results of dissolution testing Percentage dissolved in minutes						
Sampling time (min)	Test product Torsemide Tablets 5 mg, Lot # K26694			Reference Product Demadex® Tablets 5 mg, Lot # 0005-50, Exp. 10/02		
	Mean	Range	%CV	Mean	Range	%CV
10	99	_____	2.0	99	_____	4.1
15	98	_____	2.0	100	_____	4.5
30	98	_____	1.5	99	_____	3.6
45	98	_____	1.3	100	_____	4.1
Sampling time (min)	Test product Torsemide Tablets 10 mg, Lot # K26695			Reference Product Demadex® Tablets 10 mg, Lot # 0012 Exp. 10/02		
	Mean	Range	%CV	Mean	Range	%CV
10	94	_____	2.1	98	_____	1.8
15	96	_____	0.9	98	_____	1.8
30	96	_____	0.6	98	_____	2.1
45	96	_____	0.6	98	_____	3.4
Sampling time (min)	Test product Torsemide Tablets 20 mg, Lot # K26696			Reference Product Demadex® Tablets 20 mg, Lot # 0077 Exp. 10/02		
	Mean	Range	%CV	Mean	Range	%CV
10	93	_____	2.7	97	_____	2.3
15	94	_____	2.7	98	_____	1.8
30	95	_____	2.2	98	_____	1.8
45	96	_____	1.7	98	_____	1.7

WAIVER REQUEST ON THE HIGHER STRENGTH:

On February 23, 2001, the firm submitted a waiver request on the 100-mg strength of torsemide tablets. In support of this waiver, the firm has provided comparative formulation of its 20-mg and 100-mg torsemide tablets, and dissolution testing on the 100-mg test and reference tablets.

Formulation (Not to be released under FOI)

Comparative Components and Composition of Teva's 20- and 100-mg Torsemide Tablets

	Amount: mg/tablet	
	20-mg Strength	100-mg Strength
Torsemide	20.0	100.0
Lactose Anhydrous NF		
Crospovidone, NF		
Povidone, USP		
Microcrystalline Cellulose NF		
Magnesium Stearate, NF		
Total Weight	400.0	400.0

Comments on Formulation: (Not to be released under FOI)

1

2. All inactive ingredients utilized in the formulation are within the listed levels in the Inactive Ingredient Guide (1996) for oral tablets.

Dissolution on 100-mg strength:

In its February 23, 2001 submission, the firm had submitted dissolution testing data using a USP type II apparatus in _____ at a speed of 50 rpm, with a dissolution specification of _____ at 30 minutes, sampling times at 10, 30 and 45 minutes. This method is the identical to that used by the firm in its original application of December 12, 2000 for the lower strength torsemide tablets.

The Agency considered the above dissolution conditions unacceptable, and requested the sponsor conduct dissolution testing using the following method (please see comments related to **Deficiency 2** above):

Apparatus: 2 (paddle), 50 rpm
Medium: 0.1N HCl, 900 mL
Sampling Times: 10, 15, 30 and 45 minutes
No. of units to be tested: 12

In the current application, the firm has provided comparative dissolution testing results on torsemide tablets 100 mg and the reference drug Demadex® tablets 100 mg using the Agency's recommended method. The dissolution results are given in the table below:

Test Products: Torsemide Tablets Dose strengths: 100 mg Reference Products: Demadex® Tablets, 100mg Assay methodology: _____						
Site of Dissolution Testing: Teva Pharmaceutical Industries Ltd. Pharmaceutical Operations Division – Research and Development KFAR SABA, ISRAEL Analysis Date: May 2001						
Results of dissolution testing Percentage dissolved in minutes						
Sampling time (min)	Test product Torsemide Tablets 100 mg, Lot # K26848			Reference Product Demadex® Tablets 100 mg, Lot # 0015, Exp. 9/02		
	Mean	Range	%CV	Mean	Range	%CV
10	93	_____	3.0	94	_____	2.0
15	94	_____	3.2	95	_____	1.6
30	95	_____	1.3	95	_____	1.8
45	95	_____	1.0	95	_____	1.7

Comments on Dissolution Testing:

1. The Agency's recommended dissolution method for torsemide tablets has the following specifications:
 NLT _____ (Q) in 15 minutes _____
2. At present an official compendial test for the Torsemide tablets does not exist. The firm has conducted dissolution testing using the Agency's recommended method. Firm's dissolution is acceptable.

RECOMMENDATIONS

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Teva Pharmaceuticals on its Torsemide 20-mg Tablet, Lot # K26696, comparing it to Demadex® 20-mg Tablet, Lot #0077 have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Teva's Torsemide 20-mg tablets are bioequivalent to the reference product Demadex® 20-mg tablets manufactured by Roche Laboratories.
2. The firm has conducted an acceptable dissolution testing on its Torsemide 20-mg Tablet, Lot # K26696.
3. The dissolution testing conducted by the firm on its Torsemide 5-mg, 10-mg and 100-mg tablets is acceptable. The firm has conducted an acceptable in vivo bioequivalence study comparing its 20-mg tablets of the test product with 20-mg tablets of the reference product Demadex® manufactured by Roche Laboratories. The formulations for the 5-mg and 10-mg strengths are proportionally similar to the 20-mg tablet of the test product, which underwent bioequivalency testing. The

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-110

**ADMINISTRATIVE
DOCUMENTS**

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION

ANDA APPROVAL SUMMARY

ANDA: 76-110

DRUG PRODUCT: Torsemide Tablets

FIRM: TEVA Pharmaceuticals USA

DOSAGE FORM: Oral Tablets

STRENGTH: 5 mg, 10 mg, 20 mg and 100 mg

cGMP STATEMENT/EIR UPDATE STATUS: Acceptable

The cGMP Statements located on pages 294-296 are satisfactory.

The overall recommendation for the Establishment Evaluation Request is acceptable (06-MAR-2001).

BIO STUDY: Acceptable 6/26/01

The recommended interim dissolution specifications are as follows:

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

Not less than \sim (Q) of the labeled amount of Torsemide is dissolved from the dosage form in 15 minutes.

VALIDATION: Pending

The drug substances and drug product are not compendial. FDA methods validation is required.

STABILITY- (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Acceptable

The containers used in the accelerated and room temperature studies are the same as proposed in the application. The firm provided 3 months accelerated conditions and 18 months controlled room temperature stability data for the packaged drug product.

The Torsemide Tablets are packaged as follows:

5 mg: 100 count; 10 mg: 100 count and 500 count; 20 mg: 100 count and 500 count; 100 mg: 100 count and 500 count.

The accelerated stability data supports TEVA's proposed tentative expiry date of 24 months.

Stability tests and specifications are as follows:

Assay:

Torseamide: ; of the labeled amount of Torsemide

Dissolution:

Not less than (Q) of the labeled amount of Torsemide is dissolved from the dosage form in 15 minutes.

Description:

5 mg: white to off-white, oval shaped tablet, scored and debossed "9" and "3" on one side of the score; on the other side debossed "7127".

10 mg: white to off-white, oval shaped tablet, scored and debossed "9" and "3" on one side of the score; on the other side debossed "7128".

20 mg: white to off-white, oval shaped tablet, scored and debossed "9" and "3" on one side of the score; on the other side debossed "7129".

100 mg: white to off-white, oval shaped tablet, scored and debossed "9" and "3" on one side of the score; on the other side debossed "7130".

LABELING Review Status: Acceptable 9/25/01

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH: Acceptable 6/26/01

TEVA manufactured one bio batch, Batch Number K-26696. This batch was used for stability studies.

Torseamide, drug substance, used in the bio batches is supplied by TEVA Tech Ltd. The drug substance is a Type II DMF # and is adequate as of 4/12/02.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

TEVA placed the following exhibit batches on stability:

5 mg: Batch Number K-26694; 10 mg: Batch Number K-26695;
20 mg: Batch Number K-26696 (Bio-Batch);
100 mg: Batch Number: K-26848

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): Acceptable

The proposed post-approval batch size is the following:

- 5 mg: _____ tablets
- 10 mg: _____ tablets
- 20 mg: _____ tablets

- No _____
- 100 mg: _____ tablets

CHEMIST: R.F. Powers, Ph.D. *RS!* DATE: *5/6/02*
Team Leader: A. Mueller, Ph.D. *RS!* DATE: *5/6/02*

cc: ANDA 76-110
Division File
Field Copy

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F/T by: DJ 5/6/02

**APPEARS THIS WAY
ON ORIGINAL**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 76110/000**
Stamp: **01-FEB-2001** Regulatory Due:
Applicant: **TEVA PHARMS**
1090 HORSHAM RD
NORTH WALES, PA 19454

Priority:
Action Goal:
Brand Name:
Established Name: **TORSEMIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **5 MG, 10 MG, 20 MG**

Org Code: **600**District Goal: **01-JAN-2002**

FDA Contacts: **T. AMES (HFD-640) 301-827-5849 , Project Manager**
A. MUELLER (HFD-623) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 06-MAR-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **9610276** DMF No:
TEVA PHARMACEUTICAL INDUSTR AADA No:
2 HAMARPE STREET
INDUSTRIAL ZONE BOX 1142, JERUS

Profile: **CTL** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE OTHER**
Last Milestone: **OC RECOMMENDATION** **TESTER**
Milestone Date: **05-MAR-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **9610275** DMF No:
TEVA PHARMACEUTICAL INDUSTR AADA No:
KFAR SAVA, , IS

Profile: **TCM** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE**
Last Milestone: **OC RECOMMENDATION** **MANUFACTURER**
Milestone Date: **06-MAR-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9613297** DMF No: **—**
TEVA TECH AADA No:
BEER SHEVA, , IS

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE**
Last Milestone: **OC RECOMMENDATION** **MANUFACTURER**
Milestone Date: **05-MAR-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

APPEARS THIS WAY
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Patent and Exclusivity Search Results from query on 020136 001.

Patent Data

Appl No	Prod Patent No	Patent No	Exp. Code
020136 001	RE34672	AUG 11,2006	

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the

Patent and Exclusivity Terms

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According to the 6/11/01 Patent Amendment, Tem was not sued within the 45-day period (expired 5/13/01)

*Verified
5/15/02*

Search results from the "Rx" table for query on "020136."

Active Ingredient: TORSEMIDE
Dosage Form;Route: Tablet; Oral
Proprietary Name: DEMADEx
Applicant: ROCHE
Strength: 5MG
Application Number: 020136
Product Number: 001
Approval Date: AUG 23, 1993
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: [Click Here](#)

Active Ingredient: TORSEMIDE
Dosage Form;Route: Tablet; Oral
Proprietary Name: DEMADEx
Applicant: ROCHE
Strength: 10MG
Application Number: 020136
Product Number: 002
Approval Date: AUG 23, 1993
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: [Click Here](#)

Active Ingredient: TORSEMIDE
Dosage Form;Route: Tablet; Oral
Proprietary Name: DEMADEx
Applicant: ROCHE
Strength: 20MG
Application Number: 020136
Product Number: 003
Approval Date: AUG 23, 1993
Reference Listed Drug: Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: [Click Here](#)

Active Ingredient: TORSEMIDE

Dosage Form;Route: Tablet; Oral
Proprietary Name: DEMADEx
Applicant: ROCHE
Strength: 100MG
Application Number: 020136
Product Number: 004
Approval Date: AUG 23, 1993
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: [Click Here](#)

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Active Ingredient Search Results from "Rx" table for query on "torsemide."

Appi No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020137		Yes	TORSEMIDE	Injectable; Injection	10MG/ML	DEMADEX	ROCHE
020136		No	TORSEMIDE	Tablet; Oral	100MG	DEMADEX	ROCHE
020136		No	TORSEMIDE	Tablet; Oral	10MG	DEMADEX	ROCHE
020136		Yes	TORSEMIDE	Tablet; Oral	20MG	DEMADEX	ROCHE
020136		No	TORSEMIDE	Tablet; Oral	5MG	DEMADEX	ROCHE

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FDA Links Searches Check Lists Tracking Links Calendars Reports Help

Pediatric Summary

Pediatric Submissions Pediatric Exclusivity Activity Pediatric Pages for Pediatric Rule

Links to: Division Reports Division Assignments by Document Division Assignments by Discipline

There are no Pediatric Submissions, there are no Documents with Pediatric Exclusivity Activity, there are no Completed Pediatric Pages for the 1998 Rule

There was no pediatric exclusivity activity listed in the database.

APPEARS THIS WAY
ON ORIGINAL

Active Ingredient Search Results from "Rx" table for query on "torsemide."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020137		Yes	TORSEMIDE	Injectable; Injection	10MG/ML	DEMADEX	ROCHE
020136		Yes	TORSEMIDE	Tablet; Oral	100MG	DEMADEX	ROCHE
020136		No	TORSEMIDE	Tablet; Oral	10MG	DEMADEX	ROCHE
020136		No	TORSEMIDE	Tablet; Oral	20MG	DEMADEX	ROCHE
020136		No	TORSEMIDE	Tablet; Oral	5MG	DEMADEX	ROCHE

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Search results from the "Rx" table for query on "020136."

Active Ingredient: TORSEMIDE
Dosage Form;Route: Tablet; Oral
Proprietary Name: DEMADEx
Applicant: ROCHE
Strength: 5MG
Application Number: 020136
Product Number: 001
Approval Date: Aug 23, 1993
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code:

Patent and Exclusivity Info for this product: [Click Here](#)

Active Ingredient: TORSEMIDE
Dosage Form;Route: Tablet; Oral
Proprietary Name: DEMADEx
Applicant: ROCHE
Strength: 10MG
Application Number: 020136
Product Number: 002
Approval Date: Aug 23, 1993
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code:

Patent and Exclusivity Info for this product: [Click Here](#)

Active Ingredient: TORSEMIDE
Dosage Form;Route: Tablet; Oral
Proprietary Name: DEMADEx
Applicant: ROCHE
Strength: 20MG
Application Number: 020136
Product Number: 003
Approval Date: Aug 23, 1993
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code:

Patent and Exclusivity Info for this product: [Click Here](#)

Active Ingredient: TORSEMIDE

Dosage Form;Route:	Tablet; Oral
Proprietary Name:	DEMADEX
Applicant:	ROCHE
Strength:	100MG
Application Number:	020136
Product Number:	004
Approval Date:	Aug 23, 1993
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	Click Here

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Patent and Exclusivity Search Results from query on 020136 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020136	001	RE34672	AUG 11,2006	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020136	001	I-206	SEP 09,2000

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Patent and Exclusivity Search Results from query on 020136 002.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020136	002	RE34672	AUG 11,2006	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020136	002	I-206	SEP 09,2000

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Electronic Mail Message

Date: 2/9/01 9:35:09 AM
From: Margo Bennett (BENNETTM)
To: See Below
Subject: FIRST GENERIC 76-110

FIRST GENERIC TORSEMIDE TABLETS, 5 MG, 10 MG AND 20 MG TEVA
RECEIVED 2-1-2001

TEAM LEADER IS AL MUELLER

THANKS,

MARGO

To: Rashmikant Patel (PATELR)
To: Florence Fang (FANGF)
Cc: Pat Beers-Block (BEERSBLOCKP)
Cc: Frank Holcombe (HOLCOMBE)
Cc: Vilayat Sayeed (SAYEEDV)
Albert Mueller (MUELLERA)

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : February 9, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

Handwritten initials: a stylized 'S' with a horizontal line through it, possibly 'S/1'.

Handwritten date: 09-FEB-2001

SUBJECT: Examination of the bioequivalence study and request for waiver submitted with an ANDA for Torsemide Tablets, 5 mg, 10 mg and 20 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j) (5) (B) (iv).

Teva Pharmaceuticals USA has submitted ANDA 76-110 for Torsemide Tables, 5 mg, 10 mg and 20 mg. The ANDA contains a certification pursuant to 21 USC 355 (j) (2) (A) (vii) (iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study and request for waiver are complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study and request for waiver submitted by Teva on February 1, 2001 for its Torsemide product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design
 - (a) Appropriate number of subjects
 - (b) Description of methodology
2. Study results
 - (a) Individual and mean data is provided
 - (b) Individual demographic data
 - (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

Study meets statutory requirements

Study does **NOT** meet statutory requirements

Reason:

Waiver meets statutory requirements

Waiver does **NOT** meet statutory requirements

Reason:

7st

Director, Division of Bioequivalence

2/27/01

Date

Application: ANDA 76110/000 Action Goal:
Stamp: 01-FEB-2001 District Goal: 01-JAN-2002
Regulatory Due: Brand Name:
Applicant: TEVA PHARMS Estab. Name: TORSEMIDE
1090 HORSHAM RD Generic Name:
NORTH WALES, PA 19454
Priority: Dosage Form: (TABLET)
Org Code: 600 Strength: 5 MG, 10 MG, 20 MG
Application Comment:
FDA Contacts: T. AMES (HFD-640) 301-827-5849 , Project Manager
A. MUELLER (HFD-623) 301-827-5848 , Team Leader

Overall Recommendation:

Establishment: 9616777

TEVA PHARMACEUTICAL INDUSTRIAL LTD
2 HAMARPE STREET
HAR-HOTZVIM, JERUSALEM, IS

DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: WILL PERFORM RELEASE AND STABILITY TESTING. (on 05-MAR-2001 by P.
PATEL (HFD-615) 301-827-5862)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-MAR-2001				PATELP

Establishment: 9610275

TEVA PHARMACEUTICAL INDUSTRIES LTD
KFAR SAVA, , IS

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-MAR-2001				PATELP

Establishment: 9613297

TEVA TECH
BEER SHEVA, , IS

DMF No: 15222 AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-MAR-2001				PATELP

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-110

CORRESPONDENCE

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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

April 16, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT

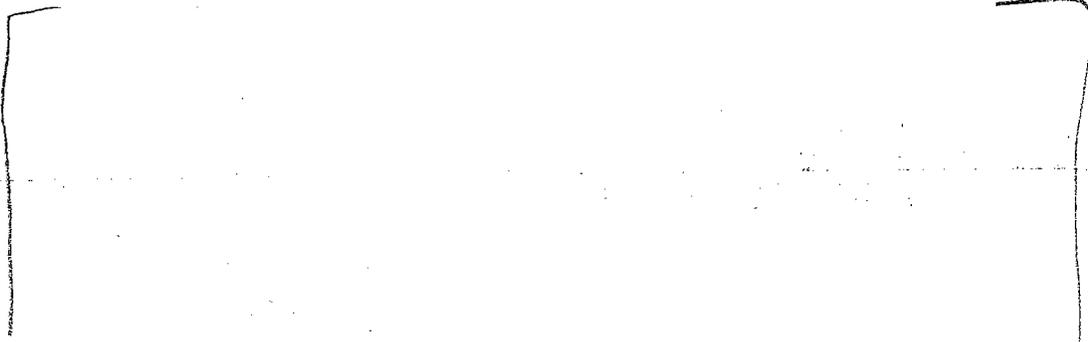
ORIG AMENDMENT
N/A/M

ANDA #76-110
TORSEMIDE TABLETS 5 mg, 10 mg, 20 mg, and 100 mg
MINOR AMENDMENT – RESPONSE TO APRIL 5, 2002 REVIEW LETTER

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith a minor amendment to the above-referenced ANDA in response to the April 5, 2002 review letter received from the Office of Generic Drugs (OGD). For ease of review the responses to your comments are addressed in the order in which they were presented in your review letter. A copy of this letter is enclosed in **Attachment 1**.

A. Chemistry Deficiencies



Information is also provided in two separately bound copies for your use.

2. Teva-Tech Ltd., the holder of drug master file No. — for Torsemide, responded to an FDA deficiency letter on April 1, 2002. Please find in Attachment 6 the cover letter to the response from Teva-Tech Ltd. In response to this DMF deficiency the

RECEIVED
APR 17 2002
OGD / CDER

NW
4/19/02

_____ (Form II) specification has been tightened and the method for _____ Content (HPLC) has been updated. Please note that since Teva Pharmaceuticals Industries Ltd. utilizes the same specifications and methods as Teva-Tech Ltd. the Teva Pharmaceuticals Industries Ltd. Torsemide specifications have been revised accordingly. Also provided in Attachment 6 is a confirmation letter stating that there is no new FDA deficiency letter for DMF No. _____

B. Notes and Acknowledgments

1. Please find current controlled room temperature stability data (up to 18 months) for each strength of Torsemide Tablets in **Attachment 7**.
2. Please note that Teva-Tech Ltd. is committed to inform TEVA of any changes made to the release and stability specifications for the drug substance.

This information is submitted towards the continued review and approval of this pending application. It is TEVA's belief that the enclosed is a complete response to the April 5, 2002 review letter. Should you have any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/cj
Enclosure



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

ANDA # 76-110

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

MINOR AMENDMENT - RESPONSE TO APRIL 5, 2002 REVIEW LETTER

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

April 16, 2002
Date



1/20/02 - AM noted - to circ Reviewer for review. [Signature]

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

January 22, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT

MINOR AMENDMENT [Signature]

ANDA #76-110
TORSEMIDE TABLETS, 5 mg, 10 mg, 20 mg, and 100 mg
MINOR AMENDMENT – RESPONSE TO DECEMBER 12, 2001 REVIEW LETTER

Dear Mr. Buehler:

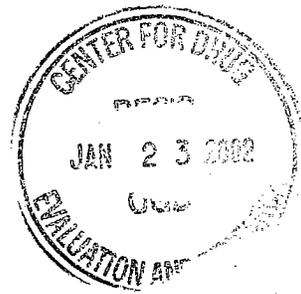
TEVA Pharmaceuticals USA submits herewith a minor amendment to the above-referenced ANDA in response to the December 12, 2001 review letter received from the Office of Generic Drugs (OGD). Please note that the comments in the review letter, a copy of which is provided in **Attachment 1**, are addressed in the order presented by OGD.

A. Deficiencies

1-2.



Attachment 3.



[Signature] 1/29/02

3. Please find in **Attachment 3** an updated method validation package for Torsemide Tablets, including the dissolution method recommended by the Division of Bioequivalence. (Dissolution data using the updated dissolution method can be found in the updated stability reports included in **Attachment 5**).
4. In response to comment #4, the difference in method numbering is simply a difference in format between the research and development analytical laboratory and the quality control laboratory. The R & D analytical laboratory develops all methods used for the drug product and tests the validity of these methods as well as their stability indicating nature. The numbering format used in this laboratory is SI-XXXXX. Once established, the R & D analytical laboratory methods are used for the stability studies and for the release of the pivotal lots. Reports of the validation studies for these R & D methods are issued separate from the method itself. The numbering of the validation reports is accomplished by inserting a “V” between the SI and the numerical portion of the corresponding method (SI-V-XXXXX). Next, a technology transfer is completed to the quality control laboratory. A monograph for the finished product, which includes the same methods established in the R & D analytical laboratory, is issued by the QC laboratory. This monograph is used for the release of the production lots. The numbering format for methods issued in the quality control laboratory had been AM-PRXXXX at the time of original submission. Since this time, the format employed by the QC laboratory has been updated and follows the format of PR-XXXX. Please find in **Attachment 4** a revised QC laboratory monograph (PR-0106, Ed. 05) which will be used for the production lots. We have deleted the wording, “for release and stability studies” from the header as the method is applicable only to the release testing of the drug product.
5. Please find in **Attachment 5** an updated finished product stability protocol for the 100 mg dose strength in which the appearance description was updated. In addition, we have included updated stability reports for each dose strength, which reflect the revised dissolution specification and description of appearance.
6. Please find in **Attachment 5** the revised stability reports. Also provided as **Attachment 6** is a summary of specifications for the drug product revised per your recommendations.

7. The holder of drug master file No for torsemide responded to the FDA on November 28, 2001. Please find in **Attachment 7** the cover letter of the response from Plantex USA, Inc. Also included in this attachment is a revised specification sheet for the active drug substance, torsemide, Edition 03, as requested by the FDA. The revision reflects the addition of reference to Organic Volatile Impurities and a statement that none of the solvents specified in the USP General Chapter are used in the synthesis of the A.P.I.

It is TEVA's belief that the enclosed is a complete response to the December 12, 2001 review letter. Should you have any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson | U.A.

PE/asg

Enclosure



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

ANDA # 76-110

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

MINOR AMENDMENT - RESPONSE TO DECEMBER 12, 2001 REVIEW LETTER

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.

Philip Erickson, R.Ph.

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms



1/22/2002

Date



AM noted, to CMC
Review for review.
Purs 9/14/01

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

ORIG AMENDMENT
N/AM

September 4, 2001

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



MINOR AMENDMENT

ANDA # 76-110
TORSEMIDE TABLETS, 5 mg, 10 mg, 20 mg and 100 mg
MINOR AMENDMENT - RESPONSE TO JULY 27, 2001 REVIEW LETTER

Dear Mr. Buehler,

We submit herewith a minor amendment to the above-referenced pending ANDA. The subject of this amendment is our response to comments from the Office of Generic Drugs (OGD) pertaining to this application. The responses to your comments are addressed in the order in which they were presented in your review letter dated July 27, 2001. A copy of this letter is enclosed in **Attachment 1**.

A. Chemistry Deficiencies

[]

2. Our proposed assay acceptance range of _____ for the Torsemide raw material reflects the limits set forth in the US Pharmacopeial Forum, Volume 27 (1) January to February 2001, page 1821. As such, this methodology is under consideration by the USP Committee of Revision for official adoption. As a result, we propose maintaining this range until USP or PF proposes a different specification.

3. Per your request, we have revised our specifications to differentiate between _____ Please find enclosed, as **Attachment 3**, a revised Certificate of Analysis, the Torsemide API release method which includes the determination of _____ testing and the revised Residual Solvents method and validation. Torsemide drug substance lot 821700100 has been re-evaluated for _____. As evidenced by the enclosed CofA, lot 821700100 has been identified as _____ (**Attachment 4**).
4. Please refer to the _____ response letter dated August 13, 2001 addressing deficiencies regarding DMF _____. A detailed description and characterization for the drug substance reference standard, lot 8517ST02-MK-594, has been provided therein. Please note that Teva-Tech Ltd. (TEVA Group API Division) is a wholly owned subsidiary of TEVA Pharmaceutical Industries. The requested verification by means of _____ analysis of the _____ form for drug substance reference standard, lot #8517ST02-MK-594, has also been provided in **Attachment 4**.
5. Upon receipt, the Teva-Tech Ltd. material does undergo at least one ID test. The Teva Certificate of Analyses of our _____ facility for the active ingredient used to manufacture pivotal batches may be found on page 143 of the original ANDA and pages 84 and 89 of our new correspondence for the addition of the 100 mg strength. Please note that full monograph testing is performed on a yearly basis as part of our vendor validation program.
6. Lactose anhydrous, not _____ is used in our proposed drug product formulation. For lactose anhydrous to qualify as a NF material, it must meet the requirements of several tests cited in the _____ monograph. These tests include: *Identification B, Identification C, Packaging and Storage, Labelling, Clarity and Color of Solution, Specific rotation <781>, _____ <61>, _____ Residue on Ignition <281>*, and _____ *Impurities*. Therefore, both monographs were included in our application.

7.



for your review as **Attachment 5**.

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_____ can be monitored per the proposed in-process
_____ test.

19. According to the ICH guideline Q3C Impurities: Residual Solvents, "If only class 3 _____ are present, a non-specific method such as _____ may be used." Consequently, _____ can be monitored per the proposed in-process _____ test.
20. Please find enclosed, in **Attachment 12**, the characterization and identification of the reference standards that were used throughout the drug substance validation. Two reference standards were used for the drug product. The primary reference standard (control number 8517ST02-MK-594) and the secondary standard (control number 8517ST02-MK-654), characterization and identification can also be found in **Attachment 12**.
21. Please find attached the stability reports for the 100 mg strength. (**Attachment 13**)

B. Notes and Acknowledgments

1. Teva acknowledges that satisfactory method validation for the methods used in the ANDA are required. Copies of the validation commitments provided in the original ANDA and in our new correspondence for the addition of the 100 mg strength have been enclosed as **Attachment 14**. Upon request, samples will be sent to the District Office once the analytical test and specification issues are resolved.
2. We note and acknowledge that our response must address labeling deficiencies (see below).
3. Please find attached the additional stability data for the 5 mg, 10 mg and 20 mg strengths. (**Attachment 15**)

C. Bioequivalence

We note that the Division of Bioequivalence has completed its review and has no further questions at this time, however we also recognize that the bioequivalency comments provided in the July 27, 2001 review letter are preliminary, and are subject to revision after review of the entire application. Please note that dissolution testing has been incorporated into our stability and quality control programs, as specified in USP. Additionally, we provide herewith, as **Attachment 16**, the following documentation to reflect our change to the recommended dissolution test methodology:

- Revised finished product monograph (AM-PR0106)
- Updated dissolution stability indicating method (SI-17043)

- Updated dissolution analytical method validation report (VR-SI-17043, Ed. 01)
- Release Specifications and Finished Product Stability Protocols for each strength

D. Labeling

Container Labeling: (5 mg, 10 mg, 20 mg): We note that container labels for bottles of 100, and 500 tablets, as submitted in draft in the February 1, 2001 submission are satisfactory. This labeling has been updated to remain current with the innovator labeling posted on the Center for Drug Evaluation and Research's labeling website. Please find enclosed in **Attachment 17** twelve copies of final print container labels.

Container Labeling: (100 mg): We note that container labels for bottles of 100, and 500 tablets, as submitted in draft in the February 23, 2001 submission are satisfactory. This labeling has been updated to remain current with the innovator labeling posted on the Center for Drug Evaluation and Research's labeling website. Please find enclosed in **Attachment 17** twelve copies of final print container labels.

- **Patient package insert labeling:** As requested, we have revised the package insert labeling to coincide with the mock-up copy provided in your review letter dated July 27, 2001. Please find enclosed as **Attachment 18** twelve copies of final print insert labels and the requested side-by-side comparison annotating the differences between our proposed labeling with our previously submitted labeling.

It is TEVA Pharmaceutical USA's belief that the above is a full and complete response to the comments set forth in the Agency's July 27, 2001 review letter. We look forward to your continued review and approval of ANDA #76-110. Should there be any questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jmc

Enclosures



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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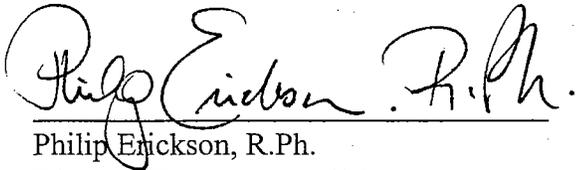
Phone: (215) 591 3000
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ANDA # 76-110

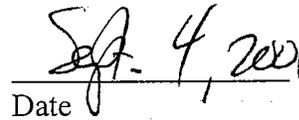
TORSEMIDE TABLETS, 5 mg, 10 mg, 20 mg, and 100 mg

MINOR AMENDMENT - RESPONSE TO JULY 27, 2001 REVIEW LETTER

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.



Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms


Date



Corporate Headquarters:
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1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

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June 11, 2001

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



TELEPHONE AMENDMENT

NEW CORRESP
NC

TSI
MJS
6/21/01

ANDA # 76-110
TORSEMIDE TABLETS, 5 mg, 10 mg, 20 mg and 100 mg
TELEPHONE AMENDMENT- EVIDENCE OF RECEIPT OF NOTICE AND COMPLETION OF
45 DAY PERIOD

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above referenced pending ANDA in accord with a telephone communication between Ms. Emily Thomas of the Office of Generic Drugs and Mr. Philip Erickson, Director of Regulatory Affairs, on June 5, 2001. Per your request, we provide herein a copy of the Federal Express Detailed Tracking Form (**Attachment 1**). This form shows that the courtesy copy of the Notice of Certification of Non-Infringement for U.S. Patent No. RE 34,672 was provided to the patent holder Roche Diagnostics GMBH. This notice was delivered to the front desk at 11:16 A.M. on March 29, 2001.

Please note that the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act began on the first day after receipt of this notice by the Patent holder, Roche Diagnostics GMBH. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act was March 30, 2001, the first day after receipt of notice. This date corresponds to the March 29, 2001 date upon which the NDA holder, Hoffmann-La Roche Inc. had received their copy of the Notice of Non-Infringement. Evidence of this date was supplied to the Agency in a May 29, 2001 correspondence. As such, the 45-day clock remains unchanged from our original correspondence.

ANDA # 76-110

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

TELEPHONE AMENDMENT, EVIDENCE OF RECEIPT OF NOTICE AND COMPLETION OF 45 DAY PERIOD

Page 2 of 2

In accord with 21 CFR 314.95, TEVA Pharmaceuticals USA hereby informs FDA that the 45 day period relating to the notice of patent certification under section 505(j)(2)(A)(vii)(IV) of the Act, in connection with the above-referenced ANDA, has expired on May 13, 2001. No action for infringement of the patent within the meaning of section 505(j)(5)(B)(iii) of the Act was brought against TEVA Pharmaceuticals USA within the required 45-day period.

Resultant from Roche Diagnostics GMBH failing to undertake legal action within the 45 day period, they have waived their right to pursue future legal endeavors under the scope of the Waxman-Hatch Act regarding this patent certification.

If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/sah
Enclosures



Corporate Headquarters:

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North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

ANDA # 76-110

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

**TELEPHONE AMENDMENT - EVIDENCE OF RECEIPT OF NOTICE AND
COMPLETION OF 45-DAY PERIOD**

In accord with the 21 CFR-314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 11, 2001

Date





Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

NEW CORRESP

NC

May 29, 2001

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



PATENT INFORMATION

ISI
MI
6/1/01

ANDA # 76-110

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

NOTICE OF CERTIFICATION, RECEIPT OF NOTICE AND COMPLETION OF 45 DAY PERIOD

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement for U.S. Patent No. RE 34,672 was provided to the holder of NDA 20-136 for Demadex® (Torsemide) Tablets, Hoffmann-La Roche Inc., in accord with 314.95(b). The notice dated March 27, 2001 contains the information as required under 314.95(c). A copy of the notice (*Attachment 1*) is provided herein. In addition, a courtesy copy (*Attachment 2*) was provided to the patent assignee, Roche Diagnostics GMBH.

In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA is hereby providing documentation of the receipt of Notice of Certification for U.S. Patent No. RE 34,672. Notice sent to the affected NDA holder, Hoffman-La Roche Inc., was received on March 29, 2001. This date is evidenced by the attached copy of the return receipt (*Attachment 3*). Please note that the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act will begin the first day after receipt of this notice by the NDA holder, Hoffman-La Roche Inc. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is March 30, 2001, the first day after receipt of notice.

In accord with 21 CFR 314.95, TEVA Pharmaceuticals USA hereby informs FDA that the 45 day period relating to the notice of patent certification under section 505(j)(2)(A)(vii)(IV) of the Act,

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ANDA # 76-110

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

NOTICE OF CERTIFICATION, RECEIPT OF NOTICE AND COMPLETION OF 45 DAY PERIOD

Page 2 of 2

in connection with the above-referenced ANDA, has expired on May 13, 2001. No action for infringement of the patent within the meaning of section 505(j)(5)(B)(iii) of the Act was brought against TEVA Pharmaceuticals USA within the required 45-day period.

Resultant from Hoffmann-La Roche Inc. failing to undertake legal action within the 45 day period, they have waived their right to pursue future legal endeavors under the scope of the Waxman-Hatch Act regarding this patent certification.

If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jmc

Enclosures



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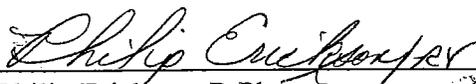
Phone: (215) 591 3000
FAX: (215) 591 8600

ANDA # 76-110

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

**NOTICE OF CERTIFICATION, RECEIPT OF NOTICE
AND COMPLETION OF 45 DAY PERIOD**

In accord with the 21 CFR 314.94(d)(5), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.


Philip Erickson, R.Ph.

Director, Regulatory Affairs
Solid Oral Dosage Forms



5/29/01
Date



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

May 16, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773



N/AB
ORIG AMENDMENT
BIOEQUIVALENCY
AMENDMENT

ANDA # 76-110
TORSEMIDE TABLETS, 5 mg, 10 mg, 20 mg and 100 mg
BIOEQUIVALENCY AMENDMENT - RESPONSE TO MAY 2, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above referenced pending Abbreviated New Drug Application in response to a review letter dated May 2, 2001. A copy of the letter is provided as **Attachment 1**. The comments are addressed in the order in which they were presented:

1. Please find in **Attachment 2** an amendment to the bioequivalency study report which contains data to support the long-term stability of Toremide in frozen study samples for a period of 151 days.
2. As requested, please find in **Attachment 3**, the dissolution test results for all strengths of Toremide Tablets versus Demadex[®] using the method recommended in the May 2, 2001 review letter. Please note that we have included dissolution test results for the 100 mg tablet strength in addition to the 20 mg, 10 mg, and 5 mg. This strength was added to our pending ANDA on February 23, 2001.

It is Teva Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the comments set forth in the May 2, 2001 review letter. This information is submitted for your continued review and approval of ANDA #76-110. If there are any further questions, please do not hesitate to contact me directly at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmc
Enclosures

ANDA 76-110

MAR 5 2001

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
|||||

Dear Sir:

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

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

DATE OF APPLICATION: February 1, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 1, 2001

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 Gregory Davis, 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:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,


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

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Page(s) of trade

secret and /or

confidential

commercial

information



Corporate Headquarters:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
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Phone: (215) 591 3000
FAX: (215) 591 8600

February 23, 2001

76110

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

ORIG AMENDMENT

N/AA

TORSEMIDE TABLETS, 5 mg, 10 mg and 20 mg
NEW CORRESPONDENCE TO ANDA SUBMITTED ON FEBRUARY 1, 2001
ADDITION OF 100 mg TABLET STRENGTH

Dear Mr. Buehler:

We submit herewith a new correspondence to the above referenced ANDA for Torseמידe Tablets, 5 mg, 10 mg and 20 mg. The subject of this submission is the addition of the 100 mg strength for this drug product. To facilitate your review, we have presented the information in the basic format of our original application.

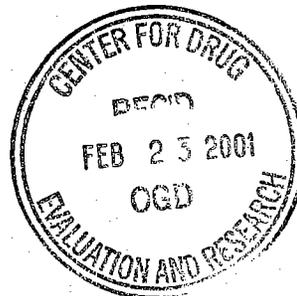
In support of this correspondence, we have provided Chemistry, Manufacturing, and Controls (CMC) documentation relevant to the 100 mg tablets, and updated CMC documentation applicable to the 5 mg, 10 mg and 20 mg tablets. In addition, a request for waiver of *in-vivo* bioavailability studies is provided in the section entitled "Bioavailability/Bioequivalence". The patent certification and exclusivity statement included in our original application also pertains to the 100 mg strength. Please reference page 12 of our original submission dated February 2, 2001.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jmc
Enclosures





Corporate Headquarters:
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1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

February 1, 2001

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

505(b)(2)(A) OK
05-MAR-2001
JSL

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
TORSEMIDE TABLETS, 5 mg, 10 mg and 20 mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Torsemide Tablets, 5 mg, 10 mg and 20 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 19 volumes; 9 for the archival copy and 10 for the review copy.

The application contains full reports of two *in vivo* bioequivalence studies. These studies compared Torsemide Tablets, 20 mg manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, Demadex[®] under both fasting and post-prandial conditions.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jmc
Enclosures

