CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20136/S009 and 20137/S008

Trade Name: DEMADEX

Generic Name: Torsemide

Sponsor: Boehringer Mannheim

Approval Date: September 9, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20136/S009 and 20137/S008

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)	X			
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EA/FONSI			X	
Pharmacology Review(s)			X	
Statistical Review(s)			X	
Microbiology Review(s)				X
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20136/S009 and 20137/S008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-136/S-009
20-137/S-008

SEP 9 1997

Boehringer Mannheim Corporation
Therapeutics
Attention: Claes Helmers, M.D., Ph.D.
101 Orchard Ridge Drive
Gaithersburg, MD 20878

Dear Dr. Helmers:

Please refer to your May 3, 1996 supplemental new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Demadex (torsemide) Tablets (NDA 20-136) and Injection (NDA 20-137).

We acknowledge receipt of your amendments dated August 15, 1997 (both applications).

The supplemental applications provide for the use of Demadex (torsemide) Tablets and Injection for the treatment of edema associated with chronic renal failure.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective for use as recommended in the final printed labeling included in the August 15, 1997 submissions. Accordingly, the supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HF-2/MedWatch (with draft/final labeling)
HFD-2/MLumpkin (efficacy supplements only)
HFD-101 (efficacy supplements only)
HFD-92 (with draft/final labeling)
HFD-110
HFD-40 (with draft/final labeling)
HFD-613 (with draft/final labeling)
HFD-735 (with draft/final labeling)
DISTRICT OFFICE
~~HFD-~~810/New Drug Chemistry Division Director
HFD-110/GBuehler/8/26/97
sb/8/26/97;9/5/97
R/D: FZielinski/9/2/97
RWolters/9/3/97
JPelayo/9/3/97
SChen/9/3/97
NMorgenstern/9/4/97

Approval Dates: 8/23/93 (both)

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20136/S009 and 20137/S008

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-136/S-009
20-137/S-008

APR 11 19[illegible]

Boehringer Mannheim Pharmaceuticals Corporation
Attention: Ms. Jayne Peterson
101 Orchard Ridge Drive
Gaithersburg, MD 20878

Dear Ms. Peterson:

Please refer to your May 3, 1996 supplemental new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Demadex (torsemide) Tablets (NDA 20-136) and Injection (NDA 20-137).

We acknowledge receipt of your amendments dated March 25, 1997 (both applications).

The supplemental applications provide for the use of Demadex (torsemide) Tablets and Injection for the treatment of edema associated with chronic renal failure.

We have completed the review of these supplemental applications as submitted with draft labeling and they are approvable. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft. In addition, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submissions, please provide highlighted or marked-up copies that show the changes that are being made.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the FPL may be required.

Please submit sixteen copies of the printed labeling to each application ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw these supplemental applications.

These changes may not be implemented until you have been notified in writing that these supplemental applications are approved.

Should you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
Telephone: (301) 594-5332

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-2/MLumpkin (efficacy supplements only)
HFD-92
HFD-101 (efficacy supplements only)
~~HFD-110~~
HFD-110/Project Manager
~~HFD-40/DDMAC (with~~ labeling)
DISTRICT OFFICE
HFD-110/GBuehler/3/14/97;4/8/97
sb/3/18/97;4/10/97
R/D: CCoughlin/4/8/97
RWolters/4/9/97
SChen/4/9/97
NMorgenstern/4/10/97

Approval Date: 8/23/93 (both applications)

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER : 20136/S009 and 20137/S008

—

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

MAR 4

NDA #: 20-136/SE2-009; 20-137/SE2-008
DRUG NAME: Demadex® (torsemide)
SPONSOR: BOEHRINGER MANNHEIM Pharmaceuticals Co.
TYPE OF DOCUMENT: New Drug Application/Supplemental Application-Labeling Change
DATE RECEIVED: 05/06/96
DATE REVIEW COMPLETED: 03/04/97
MEDICAL REVIEWER: Juan Carlos Pelayo, M.D.

INTRODUCTION

Boehringer Mannheim Corporation has submitted this supplemental application to NDA 20136 seeking approval for a labeling change of Demadex® (torsemide) tablets and injection, on the basis of the results of study No. TOR-64 (MF 8264), report No. OU-117.

Demadex®, a diuretic that inhibits the $Na^+2Cl^-K^+$ carrier system in the thick ascending limb of the loop of Henle, is currently approved for the treatment of edema associated with renal disease. The current labeling however, indicates that "chronic use of any diuretic in renal disease has not been studied in adequate and well-controlled trials."

Thus, the sponsor designed the present study, with the concurrence of the FDA, "to show that, in patients with chronic renal insufficiency, torsemide is effective in preventing fluid reaccumulation when administered over a period of time long enough to achieve a steady state fluid balance." According to the sponsor the FDA, that is the Division of Cardio-Renal Drug Products, agreed that if they show efficacy in this study, the protocol design was acceptable to support a claim for long-term effectiveness in renal disease.

GENERAL INFORMATION

Name of Drug: Generic: Torsemide; Trade: Demadex®; Chemical: 1-isopropyl-3-[(4-*m*-toluidino-3-pyridyl)sulfonyl]urea.

Pharmacologic category: "Loop" diuretic.

Proposed indication: Chronic use in the treatment of edema associated with renal failure.

Dosage form and route of administration: Twenty and 100 mg tablets, 20-200 mg p.o. QD or 200 mg p.o. BID.

Related drugs: Lasix® (furosemide).

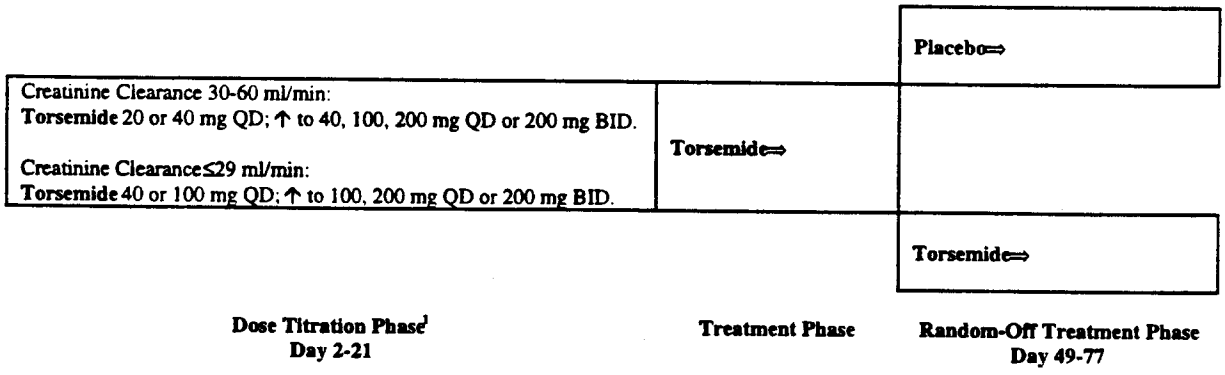
CLINICAL STUDY/TOR-64 (MF8264)

METHODS

Primary Objective: To demonstrate the long-term effectiveness of therapy with oral torsemide in patients with chronic renal insufficiency (CRI) who are at steady state with respect to fluid balance.

Experimental Design: This was a multi center, randomized, placebo controlled, parallel, double-blind study, in patients with stable chronic renal insufficiency. The clinical trial was performed in three phases: a torsemide dose titration phase, a torsemide treatment phase, and a random-off treatment period during which patients were assigned randomly and in double fashion either to continue torsemide at a stable dose or switch to placebo (Figure 1). Twenty and 40 mg were the initial doses for patients with creatinine clearance of 30-60 ml/min and ≤29 ml/min, respectively. Torsemide was titrated up to a level adequate to produce "an optimal therapeutic state regarding body weight and edema." They titrated dosages to 40 mg, 100 mg, and 200 mg once daily. If necessary, a second dose of 200 mg followed a daily dose of 200 mg given twelve hours apart. They randomly assigned patients to one of the two treatments during the random-off treatment period.

Figure 1. Experimental Design



[1] Titration to a stable dosage of torsemide, sufficient to produce an optimal state with regard to body weight and edema, was to be completed by Visit 3 (day 21).

Blinding: The torsemide titration and stable dose treatment phases were open-label. However, the random-off treatment period was randomized, double blind and placebo controlled. At visit seven, they randomly assigned patients who met all criteria for continuing in the study to receive torsemide at the same dose as received in the stable period, or to receive identically appearing placebo in a double-blind fashion.

Study Population: The study population was comprised of patients with chronic renal failure. They planned to enroll approximately 30 patients to each treatment group[2].

Subject Selection: The inclusion and exclusion criteria utilized in subject selection are described below.

Inclusion Criteria

- Age range: 18 or older.
- Patients with stable chronic renal insufficiency not requiring dialysis in whom creatinine clearance (C_{cr}) must be ≤ 60 ml/min. If a creatinine clearance has not been determined within the past three months, an estimated value may be calculated using the Cockcroft-Gault formulas provided below:

  (Men) $C_{cr} = (140\text{-age}) \cdot Wt/(P_{cr} \cdot 72)$

  (Women) $C_{cr} = (140\text{-age}) \cdot Wt/(P_{cr} \cdot 85)$
- Patients must have edema or must be receiving stable doses of furosemide (40 mg or greater) or bumetanide (1 mg or greater) which were prescribed primarily for the reduction of edema.

Exclusion Criteria

- Hypersensitivity to sulfonylureas.
- Patients who have had an organ transplant or who were requiring any type of dialysis
- Patients who have had at screening a serum potassium level equal to or above the upper limit of normal at the investigator's institution.
- Patients who were known to have a diagnosis of Type IV renal tubular acidosis.
- Patients with clinical significant congestive heart failure.
- Patients with recent myocardial infarctions or other conditions where changes in fluid balance might jeopardize their safety or interfere with establishing stability of fluid balance in this study.
- Patients who at screening have a hyperchloremic acidosis defined as a serum $Cl^- \geq 110$ mEq/l and a serum $CO_2 \leq 22$ mEq/l and a serum potassium above the normal range.
- Knowledge or suspicion by the investigator that the subject abuses drugs or alcohol and would be an unreliable patient in the study.
- Women of childbearing potential who are not using a reliable form of contraception; all women of childbearing potential must have a negative pregnancy test at screening.
- Any condition or disease which in the judgment of the investigator would place the subject at undue risk or interfere with the ability of the patient to establish stability of fluid balance or to respond to a diuretic (decompensated congestive heart failure, clinically significant hepatic insufficiency, hyperthyroidism, etc.), or interfere with the ability of the patient to complete the study.
- Patients who cannot comply with the concomitant medication criteria.
- Patients with morbid obesity.
- Patients with acute urinary tract obstruction, or chronic obstruction which interferes with excretory function.
- Patients who have received an Investigational drug in another clinical trial within the past 30 days.

[2] Sample size calculation: According to the sponsor, if a standard deviation of 1.7 kg were assumed, 30 patients per treatment group would provide approximately 90% power to detect a difference of 1.5 kg in mean change from baseline between the two treatment groups. An overall significance level of 5% was assumed.

Compliance: Compliance was determined by tablet counting[3].

Primary Efficacy Endpoint: The primary variable was the change in body weight from baseline (Visit 7 immediately prior to randomization) to the last visit of the random-off period, based on measurements taken in the clinic.

Secondary Efficacy Endpoints: Secondary variables were changes from baseline to termination in patient recorded-body weight and serum potassium and in the following signs and symptoms of fluid retention: peripheral edema, rales, paroxysmal nocturnal dyspnea, and orthopnea. Other secondary variables included: the number of patients who were withdrawn from the study during the random-off period because of hyperkalemia, and the number of days from baseline to discontinuation of the study for each patient.

Safety: The occurrence of adverse events was elicited and monitored at every clinic visit. The investigator asked whether the patient had any symptoms or noticed any change in bodily function since the previous visit. All adverse events encountered during the clinical study were reported in the CRF.

Withdrawal and Replacement Criteria: Patients were informed of their right to withdraw from the study at any time for any reason. The investigator also had the right to withdraw patients from the study in the event of adverse events or poor compliance.

Concomitant Medication: Medications already prescribed, i.e., nitrates, β-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, low-dose aspirin, antiarrhythmic drugs or cardiac glycosides, for at least seven days before entry into the study were allowed to be continued. After Visit 1 (study day 1), other diuretics such as thiazides, chlorthalidone, furosemide, etc., or potassium-sparing drugs such as triamterene, amiloride, spironolactone, etc., was discontinued.

Interim Analysis: The sponsor planned an interim analysis of efficacy after approximately thirty patients have completed the study (see NDA 20136/SLR-009, Volume 1, pages 28-30).

Amendments: No amendments were incorporated by the sponsor throughout the study.

[3] If patients had taken less than 80% or more than 120% of expected medications doses: 1) at two consecutive visits during the titration and torsemide stable dose phases were considered noncompliant and were to be withdrawn from the study, 2) during the random-off treatment period were also considered noncompliant, they were coached about the importance of compliance but were not to be withdrawn from the study.

RESULTS

The first patient was randomized in the study on November 18, 1993 and the last patient completed the study on March 17, 1995. Although an interim analysis was originally entertained by the sponsor, "this was not performed because all patients had been enrolled by the time data were available for 30 patients."

Patient Randomization: Investigators in eleven medical centers in the US countries conducted the study. The list of investigators involved and the participating sites in this study are depicted in Table 1.

Table 1. Center Information/List of Investigators and Sites

Center	Principal Investigator(s)	Institution-Address Country
1	Dag Kremer, M..D. Leslie Steed, M.D.	Nephrology Research Associates, P.C. Portland, OR
2*	Jules B. Puschett, M.D.	Tulane University School of Medicine, New Orleans, LA
3	Robert J. Goldstein, M.D.	Tampa, FL
4	Lawrence J. Hak, Pharm. D.	Memphis, TN
5**	-	-
6	William E. Miller, M.D.	The Hypertension Center, Wilmington, DE
7	William B. Smith, M.D.	New Orleans, LA
8	Gaurang M. Shah, M.D.	VA Hospital, Long Beach, CA
9	N. Martin Lunde, M.D.	Minneapolis, MN
10	Andrew Whelton, M.D.	Universal Clinical Research Center, Baltimore, MD
11	Barry McLean, M.D.	Health South Medical Center, Birmingham, AL
12	J. David Wallin, M.D.	Louisiana State University, New Orleans, LA

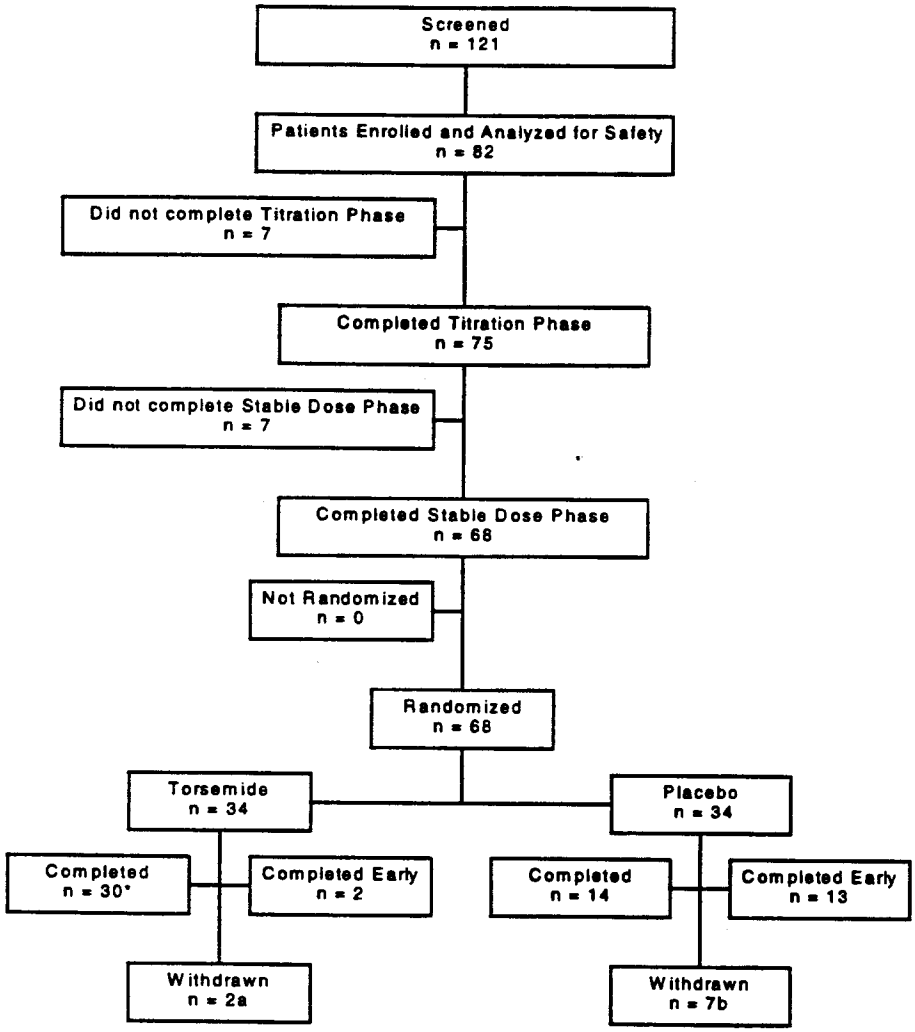
[*This center enrolled no patients in the study. **This center number was not assigned.]

Of the original twelve proposed centers, they identified eleven centers, but only ten centers screened patients. Figure 2 depicts the distribution of patients. They screened one hundred twenty-one patients. A total of sixty-eight patients entered the double-blind random-off treatment period. Fourteen patients were withdrawn during either the titration phase or stable dose phase because of an adverse event (03001, 03004, 07008, 08001, 10010, 10032), unsatisfactory therapeutic response (01002, 04006,10006, 11006), inappropriate enrollment (10017), personal reasons (10019), or noncompliance with protocol schedule (03003, 12005).

Fourteen out of 34 (41%) patients in the placebo group and 29 out of 34 (85%) patients in the torsemide group completed all visits in the double-blind period[4]. Two patients randomized to torsemide and seven patients in the placebo group were withdrawn early from the double-blind period of the study.

[4] For patient 03002, randomized to torsemide, visit 14 occurred 29 days after randomization and the patient could not return within the next several days for visit 15, thus this visit was considered the termination visit.

Figure 2. Diagram of Patient Disposition[5]



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[5] [*Patient 03002 completed visit 14 on study day 30. This was considered the termination visit.]

[aWithdrawn from torsemide in Random-off:
06002 Elective surgery
07002 Noncompliance with protocol schedule]

[bWithdrawn from placebo Random-off:
07005 Unsatisfactory therapeutic response
09003 Unsatisfactory therapeutic response
12008 Unsatisfactory therapeutic response
06001 Weight gain
07001 Increased fluid retention
11002 Shortness of breath
12009 Noncompliance with study drug]

Demographic Data: The demographic characteristics of randomized patients are summarized in the following tables. Table 2 provides a summary of sex, race, age, body weight and smoking. Considering the small number of patients studied in each group, demographic characteristics were reasonably well balanced between the groups. Exceptions to that include the greater percentage of males and blacks in the torsemide group than in the placebo group.

Table 2. Demographic Summary of All Patient Randomized

Parameter	Placebo N = 34 %	Torsemide N = 34 %
Sex		
♂	44.1	58.8
Race		
Black	52.9	64.7
White	44.1	35.3
Other	2.9	0.0
Age	(years)	(years)
Mean	63.9	64.3
Range		
Weight at Screen	(lbs)	(lbs)
Mean	174.0	185.9
Range		
Current smoker	17.7	11.8

[Sponsor's Analysis. Means were not center adjusted. NDA 20136, Volume 1, page 41.]

In Table 3 the etiologies of CRI, number of patients with clinical edema and/or on diuretics, and creatinine clearance values at screening are reported for all randomized patients. The most prevalent cause of CRI for both groups was hypertension followed by diabetic nephropathy. The distribution of etiologies of CRI, and the percentage of patients with clinical edema as well as those receiving diuretics was comparable between groups.

The attributed cause of CRI was hypertension in over 80% of the patients, and diabetic nephropathy in 20.6% and 32.4% of patients in the placebo and torsemide groups, respectively. The incidence of hypertension is significantly higher than that reported for the US population[6]. Moreover, glomerulonephritis (2.9%) as an etiology of CRI is underrepresented in this study[6]. Of note, the sponsor has ascribed more than one disease as the etiology of CRI to some patients.

A requisite for study participation was for patients to have stable chronic renal insufficiency not requiring dialysis, in whom creatinine clearance (C_{cr}) was ≤ 60 ml/min. If a creatinine clearance has not been determined within the past three months, an estimated value was calculated using the Cockcroft-Gault formulas. Of note, creatinine clearance was estimated, from serum creatinine, in sixty-one (89.7%) patients and calculated, from 24 hours urine collection and serum creatinine, in only seven (10.3%) patients (four placebo and three torsemide-treated patients). The mean values of the mostly estimated creatinine clearances were almost identical between groups.

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[6] Incidence and prevalence of ESRD (during 1993). USRDS 1997.

Etiology	% of Total
Diabetes	33.6
Hypertension	26.6
Glomerulonephritis	10.0
Cystic Kidney	2.5

Table 3. Summary of Renal History at Screening for Randomized Patients

Parameter	Placebo N = 34 n(%)	Torsemide N = 34 n(%)
Etiology of CRI:		
Hypertension	28(82.4)	28(82.4)
Diabetic Nephropathy	7(20.6)	11(32.4)
Glomerulonephritis	1(2.9)	1(2.9)
Polycystic Kidney Disease	0(0.0)	0(0.0)
Other (including unknown)	5(14.7)	5(14.7)
Edematous at screen	17(50.0)	21(61.8)
On diuretics at screen	17(50.0)	17(50.0)
Creatinine Clearance	**(ml/min)**	**(ml/min)**
Mean	39.9	38.4
Median	44.5	38.5
Range		

[Sponsor's Analysis. Means were not center adjusted. NDA 20136, Volume 1, page 42.]

Albeit, it is beyond the scope of this medical review to provide a detailed critique of the relevance of serum creatinine as a measure of glomerular filtration rate (GFR)[7], the adequacy of the Cockcroft-Gault formulas[8] to predict creatinine clearance in patients with chronic renal failure should be called into question. The original equation was derived from investigation of 249 patients, apparently all hospitalized men, **without evidence of renal disease.** An equation for women was proposed, on the basis of their ~15% lower muscle mass. Hence, the Cockcroft-Gault formulas, created for the "estimation" of creatinine clearance may **not** be applicable for the accurate prediction of creatinine clearance **in women or in patients with renal disease.** How the fact that creatinine clearance was estimated instead of measured, in sixty-one (89.7%) patients, may affect the interpretation of the results will be discussed later in this review.

Table 4 depicts mean serum creatinine values at screening for all randomized patients. As was the case for creatinine clearance, mean serum creatinine values were similar between groups.

Table 4. Summary of Mean Serum Creatinine Values at Screening for Randomized Patients

	Placebo N = 34	Torsemide N = 34
Serum Creatinine	**(mg/dl)**	**(mg/dl)**
Mean	2.32	2.35
Median	1.8	2.05
SD	1.43	1.37
Range		

[HFD-110's Analysis. Means were not center adjusted. NDA 20136, Volume 2, Appendix 11.7, pages 756-783.]

The extrapolation of creatinine clearances from serum creatinine levels in patients with chronic renal insufficiency is further confounded by the fact that downward changes in GFR at steady-state may not be reflected by parallel upward changes in serum creatinine levels before GFR has declined by ~40-60%[9].

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[7] Perrone RD, et al.: Serum creatinine as an index of renal function: New insights into old concepts. Clin Chem 38:1933-1953, 1992.

[8] Cockcroft DW, and Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 16:31-41, 1976.

[9] Shemesh O., et al.: Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int 28:830, 1985. Levey AS., et al.: Serum creatinine and renal function. Ann Rev Med 39:465, 1988.

Because of the uncertainties surrounding the validity of estimating creatinine clearance in patients with CRI by the aforementioned formula, an analysis to determine the number of randomized patients with serum creatinine within normal range and their mean serum creatinine level was performed (Table 5). Fifteen patients (44.1%) of the thirty-four patients originally randomized to each group had normal serum creatinine levels at screening. Mean (±SD) serum creatinine levels for this subgroup of patients was 1.32±0.19 mg/dl and 1.28±0.27 mg/dl in the placebo and torsemide groups, respectively (Table 5). Without an adequate measurement of renal function (i.e., GFR) at hand to argue otherwise, one could surmise that over forty percent of the patients studied had normal serum creatinine levels and probably normal renal function as well. This finding is of further concern, since this clinical investigation was supposed to study patients with chronic renal failure with creatinine clearance ≤60 ml/min at screening. Thus, the interpretation of the results may be compromised by the fact that nearly half of the patients studied may have not met the main inclusion criteria.

Table 5. Summary of Number of Patients with Mean Serum Creatinine Values Within Normal Range at Screening for Randomized Patients

	Placebo N = 34	Torsemide N = 34
Number (%) of Patients	n = 15(44.1%)	n = 15(44.1%)
Serum Creatinine	(mg/dl)	(mg/dl)
Mean	1.32	1.28
Median	1.3	1.3
SD	0.19	0.27
Range		

[HFD-110's Analysis. Means were not center adjusted. Serum creatinine normal range:
Adapted from NDA 20136, Volume 2, Appendix 11.7.1, page 745 and Appendix 11.7.3 pages 756-783.]

Next table summarizes the most frequent concomitant medications during the double blind random-off treatment period for both groups (Table 6). A higher incidence for potassium supplements, aspirin and allopurinol was documented in patients on torsemide. With regard to other medications, the frequency for clonidine was higher in the placebo group. A higher incidence of K^+ supplementation in the torsemide group than in the placebo group is in keeping with the known kaliuretic action of the drug. Nevertheless, the rather small number of patients randomized per group precludes the assessment of the significance of the overall findings.

Table 6. Summary of Most Frequent Concomitant Medications During the Double-Blind Random-off Treatment Period

Concomitant Medication	Placebo N = 34 n(%)	Torsemide N = 34 n(%)
Potassium*	3(8.8)	12(35.3)
Aspirin	6(17.6)	10(29.4)
Nifedipine	6(17.6)	8(23.5)
Insulin†	7(20.6)	8(23.5)
Clonidine	7(20.6)	3(8.8)
Allopurinol	2(5.9)	4(11.8)
Labetalol	4(11.8)	3(8.8)
Enalapril	4(11.8)	3(8.8)
Verapamil‡	10(14.7)	3(8.8)
Glyceryl trinitrate	4(11.8)	2(5.9)
Ranitidine	4(11.8)	1(2.9)

[*Includes potassium chloride, potassium, and K-Lyte†Includes insulin, insulin injection-isophane, and insulin novolin 70/30‡Includes verapamil hydrochloride and verapamil. NDA 20136, Volume 1, page 37.]

In clinical practice, other medications commonly prescribed to patients with chronic renal failure include iron, rh-erythropoietin (i.e., Epogen®, etc.), calcium and vitamin D (i.e., 1-25 $(HO)_2$ Vitamin D) supplements, phosphate "binders" (i.e., calcium carbonate, aluminum hydroxide, aluminum carbonate, etc.), and alkali therapy (i.e., sodium bicarbonate, etc.). These medications are aimed to treat the hematological and metabolic alterations associated with decreased renal function, i.e., anemia, metabolic acidosis, hyperparathyroidism, hyperphosphatemia, hypocalcemia, etc. In the vast majority of patients with CRI those hematological and metabolic alterations become obvious (i.e., measurable) when GFR decreases to approximately ≤30% of normal. A summary of concomitant medications commonly prescribed to patients with CRI during the double blind random-off treatment period is given in Table 7. Noteworthy, the number of patients requiring this therapeutics in either group was insignificant. This paucity in the incidence of "renal supplemental" treatment is in keeping with the evolving notion that the population studied in this clinical investigation had "mild" renal dysfunction.

Table 7. Summary of Concomitant Medications Commonly Prescribed for CRI During the Double-Blind Random-off Treatment Period

Concomitant Medication	Placebo N = 34 n(%)	Torsemide N = 34 n(%)
Calcium	1(2.9)	2(5.9)
Iron	1(2.9)	2(5.9)
Epoetin Alpha	1(2.9)	1(2.9)
SHOHL'S Solution	1(2.9)	1(2.9)
Aluminum Hydroxide Gel	0(0.0)	1(2.9)
Calcitriol	0(0.0)	1(2.9)
Ferrous Sulfate	1(2.9)	0(0.0)
OS-CAL	0(0.0)	1(2.9)
Sodium Bicarbonate	0(0.0)	1(2.9)
TUMS	0(0.0)	1(2.9)

[Adapted from NDA 20136, Volume 1, Table 2, pages 88-92.]

To substantiate the position that all but few of the randomized patients had "mild" renal dysfunction, the incidence at screening of abnormally high serum phosphate or low serum calcium or low serum bicarbonate was assessed (Table 8). Normal ranges for the variables measured were determined by , and the abnormal values were selected by the sponsor. As anticipated the rate of occurrence of abnormal values for those variables was small, but similar between groups. Values for hematological parameters, i.e., hematocrit, to assess anemia were not provided by the sponsor.

Table 8. Summary of Number (%) of Patients with Abnormally High Serum Phosphate or Low Serum Calcium or Low Serum Bicarbonate (Total CO_2) at Screening for Randomized Patients

Parameter	Placebo N = 34 n(%)	Torsemide N = 34 n(%)
⇑ Serum Phosphate	6(17.6)	6(17.6)
⇓ Serum Calcium	5(14.7)	5(14.7)
⇓ Serum Bicarbonate (Total CO_2)	2(5.8)	4(11.7)

[Adapted from NDA 20136, Volume 2, Appendix 11.7.2, pages 747-783.]

Table 9 provides a summary of the total daily torsemide doses at the time of randomization at visit 7 (~ Day 49), according to the treatment group to which patients were randomized. Mean values of daily torsemide doses were comparable between groups.

Table 9. Summary of the Total Daily Torsemide Doses at the Time of Randomization at Visit 7

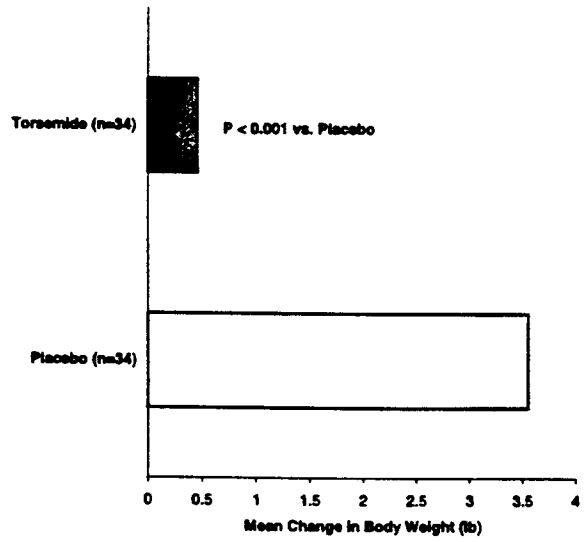
Total Daily Dose (mg)	Placebo N = 34 n(%)	Torsemide N = 34 n(%)
20	16(47.1)	10(29.4)
40	11(32.4)	15(44.1)
100	4(11.8)	6(17.6)
200	2(5.9)	2(5.9)
400	1(2.9)	1(2.9)
	(mg)	(mg)
Mean	57.6	64.7
Median	40	40

Protocol Deviations: The deviations from the protocol were minor (NDA 20136, Volume 1, page 39-41, Tables 3-5) And according to the sponsor "they do not affect the overall conclusions drawn from the study."

EFFICACY

The primary outcome was the change in body weight from baseline (Visit 7 immediately subsequent to randomization) to the last visit of the random-off period (~28 days), based on measurements taken in the clinic. Visits were scheduled to occur at peak diuretic effect. Figure 3 depicts the result of the analysis of the primary endpoint. Patients who received placebo during the random-off treatment period showed a significantly greater mean increase in body weight at endpoint than did patients who remained on torsemide, center adjusted means of 3.55 lb vs. 0.46 lb, $p<0.001$ (Sponsor's Analysis), respectively. The 95% confidence interval on this 3.09 lb difference between treatment groups is 1.87 to 4.32 lb.

Figure 3. Mean Change in Body Weight from Baseline at Endpoint - Intent to Treat Analysis



A summary of baseline body weight and change from baseline at endpoint by center is shown in Table 10. According to the sponsor, there was a significant treatment group by study center interaction ($p = 0.026$)[10]. Centers 7 and 12 were the basis for the significant interaction. Patients randomized to torsemide at center 7 gained more weight than did patients enrolled to the placebo group. An at center 12 patients receiving torsemide gained less weight than those patients receiving placebo, however the difference between groups was small.

Table 10. Baseline Body Weight (lb) and Change from Baseline at Endpoint by Center

Center	N	Placebo N=34 Mean±SD	N	Torsemide N=34 Mean±SD	Difference Mean
1 Baseline			1	235.60	
Change			1	-1.4	
3 Baseline			2	200.13±42.25	
Change			2	-0.63±0.88	
4 Baseline	3	170.83±31.63	4	152.13±42.13	
Change	3	4.58±1.38	4	0.06±1.6	4.52
6 Baseline	1	147.62	1	219.12	
Change	1	5.94	1	-2.42	8.36
7 Baseline	5	205.20±44.01	5	182.70±52.44	
Change	5	3.20±1.92	5	3.70±2.73	-0.50
8 Baseline	2	162.80±12.73			
Change	2	4.98±1.81			
9 Baseline	2	157.00±69.30	1	181.50	
Change	2	4.25±2.47	1	-0.50	4.75
10 Baseline	14	175.60±29.55	14	185.16±32.47	
Change	14	2.61±2.34	14	-0.45±2.43	3.05
11 Baseline	3	177.92±16.03	2	193.00±11.31	
Change	3	3.17±3.79	2	-1.38±1.24	4.54
12 Baseline	4	141.81±13.14	4	171.44±16.61	
Change	4	2.88±2.03	4	1.94±2.16	0.94

[Sponsor's Analysis. NDA 20136, Volume 2, Appendix 11.5.2.3, page 540. Centers 1, 3, 6, 8, & 9 were combined in the primary analysis.]

Because centers 1 and 3 randomized patients to torsemide only and center 8 enrolled patients only to placebo, the primary endpoint was analyzed excluding those centers (Table 11). Patients on the placebo arm of the study gained significantly more weight than those patients treated with torsemide.

Table 11. Change in Body Weight (lb) from Baseline at Endpoint - Centers 4, 6, 7, 9, 10, 11, 12

Center	Placebo N=32 Mean±SD	Torsemide N=31 Mean±SD	P-Value*
4, 6, 7, 9, 10, 11, 12	3.80±1.18	0.13±2.06	<0.01

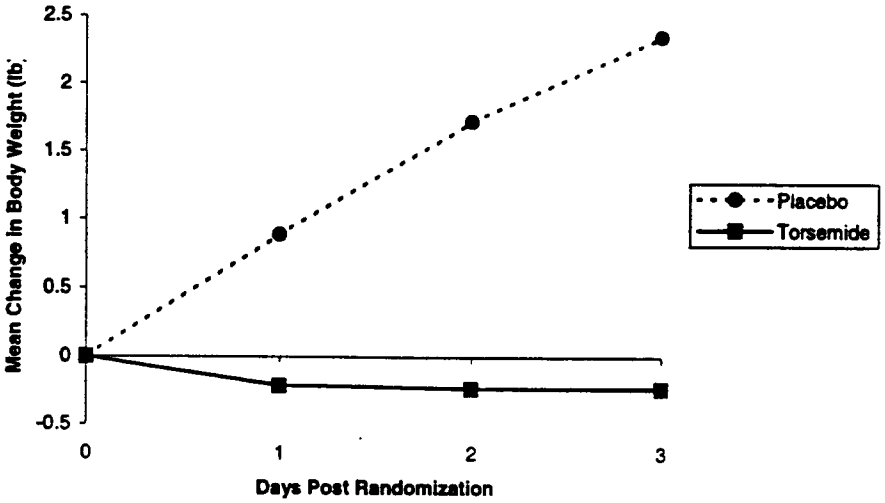
[HFD-110's Analysis. *Ttest two-sample equal variance, two-tailed distribution. Centers 1, 3, & 8 were not included in the analysis.]

As is shown in Figure 4, the mean change in body weight from baseline, by the third day after randomization, was already significantly different between the groups ($p = 0.0113$)[11]. Patients receiving placebo exhibited a steady increase in mean body weight during that period of treatment, whereas patients randomized to continue on torsemide showed no change in mean body weight.

[10] NDA 20136, Volume 1, page 45.

[11] HFD-110's analysis, Ttest two-sample equal variance, two-tailed distribution

Figure 4. Mean Change in Body Weight from Baseline to Day 3 Post Randomization[12]



In spite of the fact that the number of patients in each of the subgroups is rather small, the sponsor performed subgroup analyses by sex (Figure 5), age (Figure 6), race (Figure 7), and "creatinine clearance" at screening (Figure 8)[13]. Subgroup analysis by gender was, apparently, the only one that revealed a significant interaction (p = 0.02). The sponsor's interpretation of the subgroup analysis is "that the effectiveness of torsemide was more pronounce in women than in men." P-values for subgroup-by-treatment group interactions were 0.17, 0.28, and 0.89 for distribution by age, race, and creatinine clearance at screening, respectively.

12

Baseline	Day 1	Day 2	Day 3
Placebo n = 34	Placebo n = 31[a]	Placebo n = 31[b]	Placebo n = 25[c]
Torsemide n = 34	Torsemide n = 32[d]	Torsemide n = 32[e]	Torsemide n = 32[f]

[Sponsor's Analysis. Means were not adjusted by study center.]
[a]The decrease in number of patients represents missed visits.
[b]One patient was withdrawn due to weight gain, and two patients missed visits.
[c]One patient was withdrawn due to weight gain, one patient was withdrawn due to unsatisfactory therapeutic response, four patients completed early at investigator discretion, two patients missed visits, and one patient was withdrawn for combining open-label and double-blind study medication.
[d]The decrease in number of patients represents individual missed visits. No patients randomized to torsemide discontinued before the third day post randomization.

13 [NDA 20136, Volume 2, Appendices 11.4.4.2-5, pages 433-444.]

Figure 5. Mean Change in Body Weight from Baseline at Endpoint by Sex

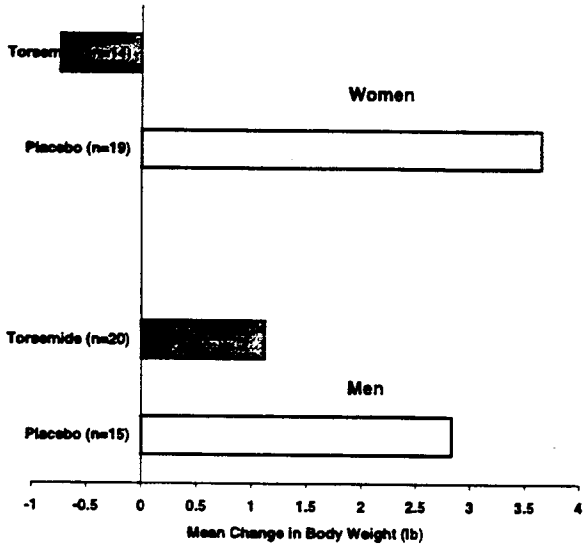


Figure 6. Mean Change in Body Weight from Baseline at Endpoint by Age

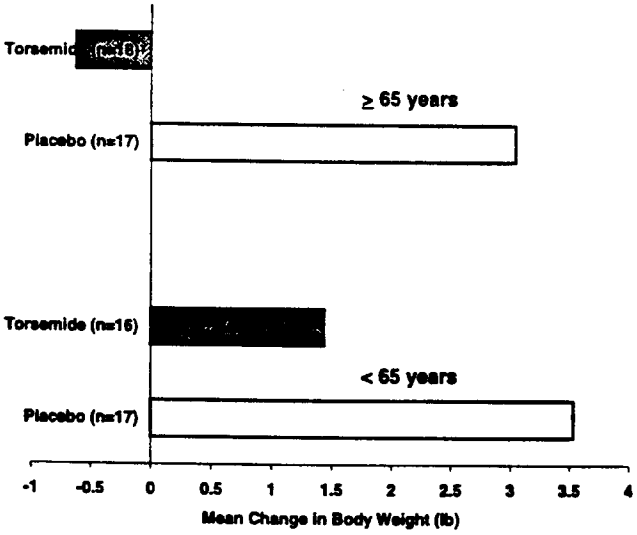


Figure 7. Mean Change in Body Weight from Baseline at Endpoint by Race

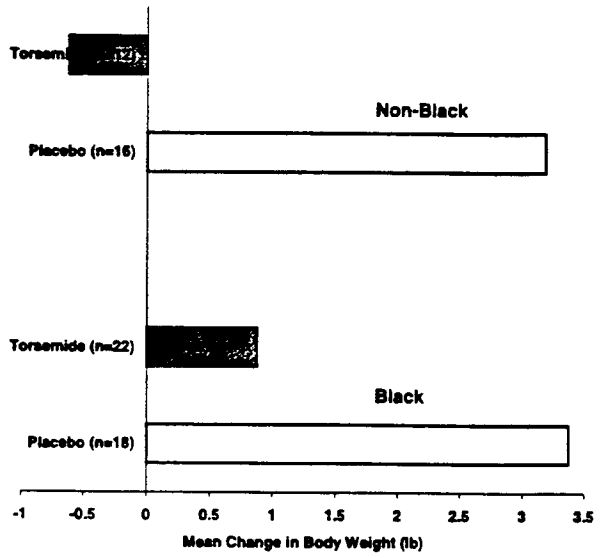
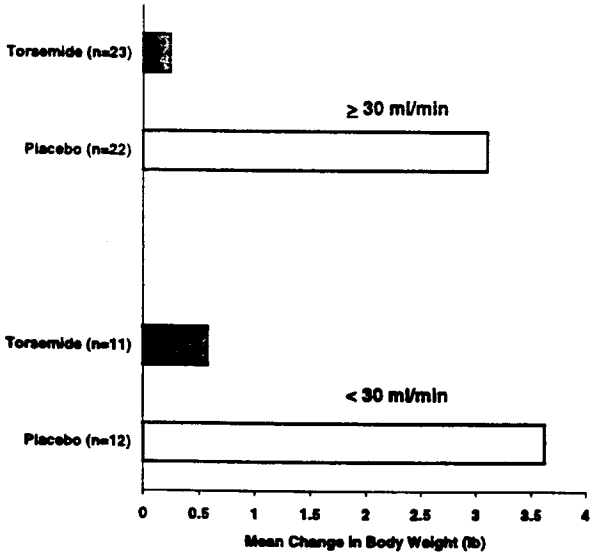


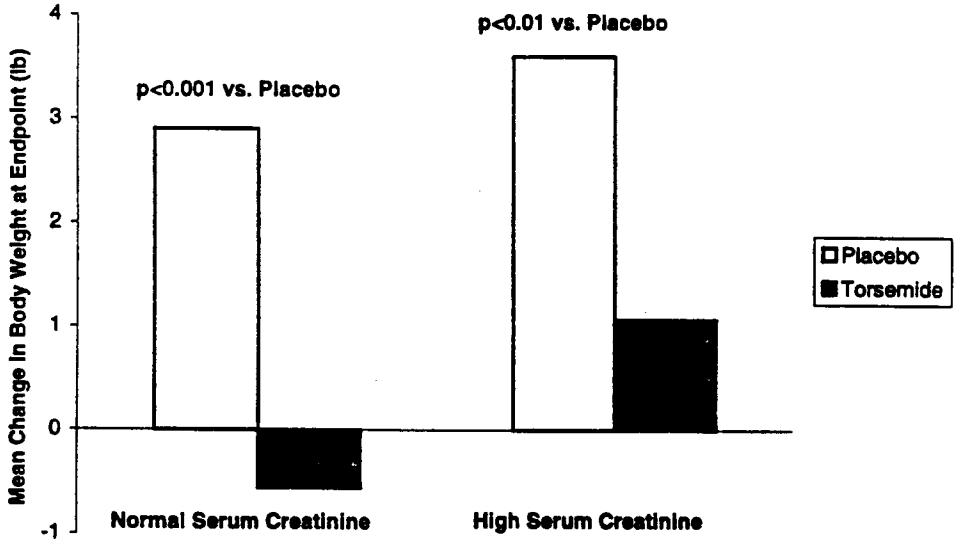
Figure 8. Mean Change in Body Weight from Baseline at Endpoint by Creatinine Clearance



Because of the distinct possibility that the diuretic effect, primarily the natriuretic effect, of torsemide may depend on the filtered load (i.e., GFR), coupled with the uncertainties of relying on an estimated creatinine clearance to assess

renal function, the effect of torsemide on mean body weight change at endpoint was re-examined based on baseline serum creatinine levels (Figure 8a, HFD-110's Analysis). Two subgroups were defined, i.e., patients with normal or abnormally high serum creatinine at baseline. Fifteen patients (44.1%) of the thirty-four patients originally randomized to each group had normal serum creatinine levels at screening; mean (±SD) serum creatinine levels for this subgroup of patients was 1.32±0.19 mg/dl and 1.28±0.27 mg/dl in the placebo and torsemide groups, respectively (Table 5). And nineteen patients randomized to each group had abnormally high serum creatinine; mean (±SD) serum creatinine level of 3.16±1.36 mg/dl for the torsemide group and of 3.16±1.43 mg/dl for the placebo group. The mean change in body weight from baseline at endpoint was significantly greater for the patients in the placebo group than for those patients in the torsemide group regardless whether the serum creatinine levels at baseline were normal (2.91±2.37 lb. and -0.56±2.39 lb., respectively, $p<0.001$) or abnormally high (3.60±2.13 lb. and 1.07±2.61 lb., respectively, $p<0.01$). The mean change in body weight in patients with normal serum creatinine was not significantly different than in those patients with abnormally high serum creatinine in the placebo group, 3.60±2.13 lb. vs. 2.91±2.37 lb., respectively, $p=0.3828$. Albeit, it was not statistically significant there was a more pronounce effect of torsemide on mean change in body weight at baseline for patients with normal serum creatinine than for those patients with abnormally high values, 1.07±2.61 lb. vs. -0.56±2.39 lb., respectively, $p=0.0696$ (HFD-110's Analysis. Ttest two-sample equal variance, two-tailed distribution). The fact that a statistically significant difference was not achieved does not negate the finding, since the study was not powered to assess how the level of renal function could affect the diuretic effect of torsemide.

Figure 8a. Mean Change in Body Weight from Baseline at Endpoint by Baseline Serum Creatinine



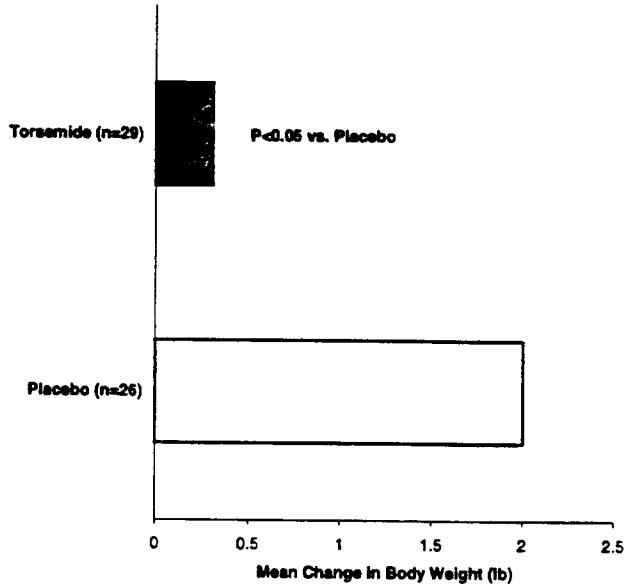
[HFD-110's Analysis. Ttest two-sample equal variance, two-tailed distribution.]

Secondary variables were changes from baseline to termination in patient recorded-body weight and serum potassium and in the following signs and symptoms of fluid retention: peripheral edema, rales, paroxysmal nocturnal dyspnea, and orthopnea. The results from the analyses of the aforementioned secondary outcomes are summarized in the following Figures and Tables.

The mean change in patient-recorded body weight from baseline to the last visit of the random-off treatment period is depicted in Figure 9. Patients were instructed to weight themselves each morning, after voiding and before taking study medication. Of note, the body weights reported by the patients were recorded at "trough", whereas the primary

analysis (Figure 3) illustrates the body weights recorded by the investigator at the "peak" diuretic effect. Patients entered in the placebo group had a mean increase in body weight of 2.00 lb, while torsemide-treated patients showed a mean increase of 0.31 lb, $p<0.05$ (Sponsor's analysis). The 95% confidence interval on this 1.69 lb difference is 0.20 to 3.16 lb.

Figure 9. Mean Change in Patient-Recorded Body Weight from Baseline at Endpoint[14]



Baseline serum potassium levels and the change from baseline at termination are summarized in Table 12. Neither significant changes nor differences between groups were observed. Three patients on placebo and 12 patients on torsemide were treated with potassium supplements.

Table 12. Baseline Serum Potassium (mEq/L) and Change from Baseline at Endpoint (mEq/L) - Intent to Treat Analysis

Period	Placebo N=33 Mean	Torsemide N=34 Mean	Difference Mean	P-Value*
Baseline	4.26	4.01	0.25	
Change	0.15	0.09	0.06	0.66

[*Sponsor's Analysis.]

Changes in the signs and symptoms of fluid retention, i.e., peripheral edema, rales, paroxysmal nocturnal dyspnea, and orthopnea, were also analyzed by the sponsor. The change in edema status for individual patients was assessed. The percentages of patients whose status worsened or was maintained/improved is provided in Figure 13. According to the sponsor, 88.2% and 79.4% of patients in the placebo and torsemide groups, respectively, had "little" or no edema at baseline. At endpoint, more patients had their status maintained/improved in the torsemide group than in

[14] Thirteen patients either did not record their body weights at all or did not record them during the double-blind period; therefore these patients (07010, 10002, 10003, 10007, 10008, 10015, 10018, 10022, 10025-29) were not included in the analysis.

the placebo group.

Figure 10. Change from Baseline in Peripheral Edema Status at Endpoint

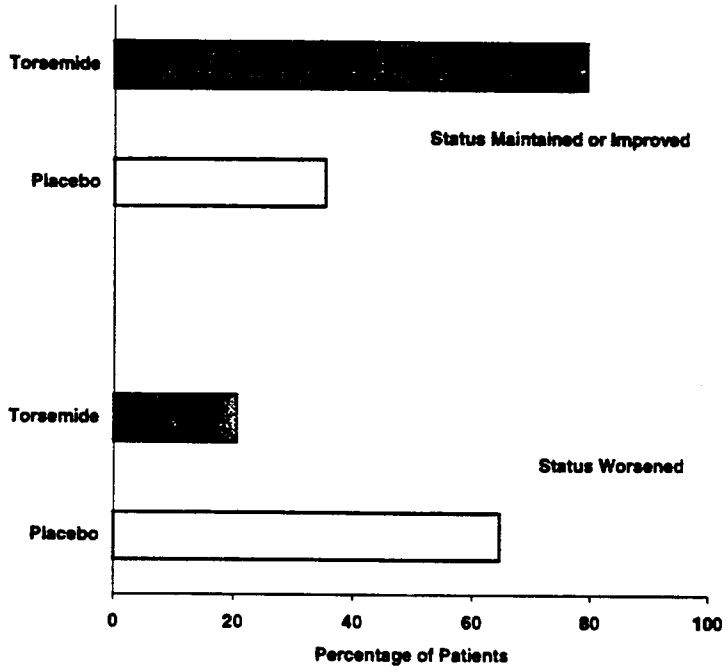


Table 13 summarizes peripheral edema status during the double-blind random-off treatment period. The sponsor's analysis demonstrated a statistically significant difference between the torsemide and placebo groups regarding the change in peripheral edema status between baseline and termination ($p<0.001$; Cochran-Mantel-Haenszel test). However, the feasibility of clinically distinguishing pitting edema between none and barely depressed, etc., needs to be called into question.

Table 13. Change in Peripheral Edema Status from Baseline at Endpoint - Intent to Treat Analysis

	Placebo N=34		Torsemide N=34	
Peripheral Edema Status	Baseline n(%)	Endpoint n(%)	Baseline n(%)	Endpoint n(%)
None	18(52.9)	9(26.5)	16(47.1)	13(38.2)
Barely Depressed	12(35.3)	6(17.7)	11(32.4)	16(47.1)
2 mm Depressed	3(8.8)	9(26.5)	6(17.7)	3(8.8)
3 mm Depressed	1(2.9)	9(26.5)	0(0.0)	1(2.9)
4 mm Depressed	0(0.0)	1(2.9)	0(0.0)	0(0.0)
≥5 mm Depressed	0(0.0)	0(0.0)	1(2.9)	1(2.9)

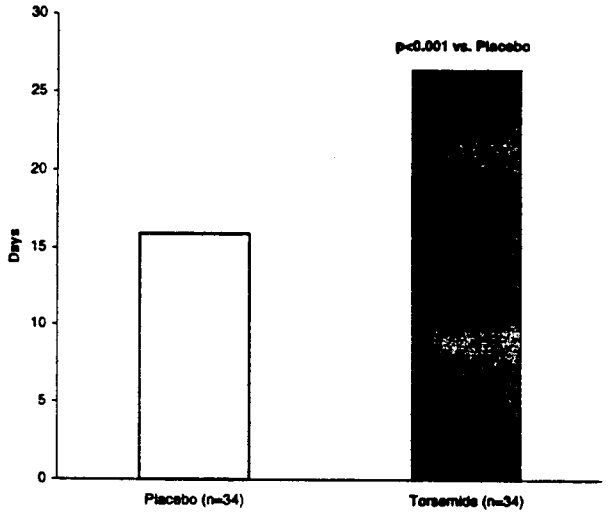
[Sponsor's Analysis. $p<0.001$ Torsemide vs. placebo; using the Cochran-Mantel-Haenszel procedure. NDA 20136, Volume 2, Appendix 11.4.4.7, pages 456-461.]

In contrast, the results of Cochran-Mantel-Haenszel analyses for rales, paroxysmal nocturnal dyspnea, and orthopnea did not show statistical significance between placebo and torsemide groups p=0.15, 0.98, and 0.35, respectively (NDA 20136, Volume 1, Tables 12-17, pages 102-107, & Volume 2, Appendix 11.4.4.8-11.4.4.10, pages 461-473

Other secondary variables included: the number of patients who were withdrawn from the study during the random-

off period because of hyperkalemia, and the number of days from baseline to discontinuation of the study for each patient. Hyperkalemia did not occur and was not a cause for discontinuation in patients from either treatment group during the double-blind period. Investigators were to keep patients in the double-blind random-off treatment period until any fluid retention was judge to be deleterious to their clinical state. The mean number of days from baseline to discontinuation of study medication is shown in Figure 11. Analysis of variance revealed a statistically significance difference in the mean number of days from baseline to discontinuation between patients treated with torsemide (range 7 to 31 days) and patients randomized to placebo (range 1 to 31 days), 26.4 vs. 15.9 days, respectively, $p<0.001$. The same analysis failed to demonstrate a significant main effect for study center ($p=0.14$), or a significant center-by-treatment group interaction ($p=0.30$).

Figure 11. Mean Number of Days from Baseline (Visit 7) to Discontinuation



Compliance: According to the sponsor, "the majority of patients were compliant with study medication within the range specified in the protocol (80-120%)."[15]

SAFETY

All eighty-two patients enrolled in the study, even if they have received one dose of torsemide, have been included in the safety analysis.

Tables 14 and 15 provide summaries of drug exposure to torsemide during the open-label titration and stable dose phases and during the double-blind random-off treatment period.

[15] [NDA 20136, Volume 2, Appendix 11.8.4, pages 855-886.]

Table 14. Summary of Exposure to Open-Label Torsemide During Titration and Stable Dose Phases

Exposure	Torsemide N = 82 n(%)
At least	
1 dose	82(100)
1 week	81(98.8)
2 weeks	80(97.6)
4 weeks	74(90.2)
6 weeks	47(57.3)
8 weeks	17(20.7)

[Sponsor's Analysis. NDA 20136, Volume 1, page 56.]

Mean torsemide exposure during the double-blind random-off treatment period was 26.6 days vs. 13.9 days for placebo.

Table 15. Summary of Exposure to Placebo and Torsemide During the Double-Blind Random-off Treatment Period

Exposure	Placebo N = 34 n(%)	Torsemide N = 34 n(%)
At least		
1 dose	34(100)	34(100)
1 week	18(52.9)	34(100)
2 weeks	14(41.2)	32(94.1)
4 weeks	11(32.4)	24(70.6)

[Sponsor's Analysis. NDA 20136, Volume 1, page 56.]

Adverse events, treatment emergent: Adverse events that had their onset during the open-label period (NDA 20136, Volume 1, Table 18, pages 108-110)and again in the double-blind random-off period were considered treatment emergent in the latter period. During the double-blind random-off treatment period, 14 (41.2%) of the patients who remained on torsemide and 12 (35.3%) of the patients who were assigned to placebo reported side effects. The most frequent treatment-emergent adverse events, regardless causality, that occurred during the double-blind random-off treatment period are summarized in Table 16 (NDA 20136, Volume 1, Table 19, pages 111-112) Comparison of the rates of individual adverse events is confounded by the fact that they were relatively infrequent and by the small number of patients studied. In keeping with the known side effects of torsemide, patients receiving the diuretic had higher rates of dizziness and hypokalemia than those in the placebo group.

Table 16. Treatment-Emergent Adverse Events, Regardless Causality, During the Double-Blind Random-Off Treatment Period

Adverse Event	Placebo N=34 n(%)	Torsemide N=34 n(%)
Hypokalemia	0(0)	3(8.8)
Dizziness	0(0)	2(5.9)
Edema	2(5.9)	0(0)
Weight Gain	1(2.9)	0(0)

[Sponsor's Analysis. NDA 20136, Volume 1, page 59.]

A list of patients with relevant/treatment related adverse events that led to concomitant medication or a dose reduction include:

- patient #06002 developed hypokalemia during titration and double-blind torsemide phases.
- patient #07003 had dizziness during titration torsemide phase.
- patient #10001 developed hypokalemia during double-blind torsemide phase.
- patient #10007 developed hypokalemia during titration and double-blind torsemide phases.
- patient #10009 developed dizziness during titration torsemide phase.
- patient #10015 developed hypokalemia during stable torsemide phase.
- patient #10023 developed dizziness during titration torsemide phase.

Deaths: Patient #04006 was a 68 year old female with a history of congestive heart failure, myocardial infarction, coronary artery bypass graft, and coronary artery disease. Hypertension was recognized as the source of her chronic renal failure. Patient was titrated to 200 mg daily and on study day 40 experienced a syncopal episode. On day 69 the patient was discontinued from the study because unsatisfactory response, i.e., weight gain, and treatment with furosemide 120 mg BID was resumed. Six days after discontinuation the patient was found dead apparently due to a cardiac arrest.

Dropouts due to adverse events: A total of nine patients were discontinued from the study because of an adverse event.

- patient #03001 on 200 mg torsemide-increased cough, dyspnea, peripheral edema.
- patient #03004 on 40 mg torsemide-acute renal failure, pyelonephritis.
- patient #07008 on 40 mg torsemide-dyspnea, chest pain, myocardial infarction, congestive heart failure.
- patient #08001 on 20 mg torsemide-weight loss, lightheadedness, increased BUN and creatinine, hypotension.
- patient #10010 on 100 mg torsemide-pruritic, papular, follicular rash.
- patient #10032 on 200 mg torsemide-syncope.
- patient #06001 on placebo-weight gain.
- patient #07001 on placebo-weight gain.
- patient #11002 on placebo-dyspnea.

Other serious adverse events: The following is a list of patients with a serious adverse event that did not lead to discontinuation from the study.

- patient #03002 on 40 mg torsemide-chest pain.
- patient #07001 on placebo-hypoglycemia.
- patient #11001 on 20 mg torsemide-fell and broke right arm.

Laboratory abnormalities: During treatment with open-label torsemide the following adverse events were reported. Two patients (07001, 11006) had episodes of both hyper- and hypoglycemia. Hypokalemia was reported by the investigators in three patients (10015, 06002, 10007). An increase in BUN and creatinine was reported in two patients (03004, 08001).

In the double-blind phase of the study the following laboratory abnormalities were reported. Hyperglycemia occurred in one patient (09003) randomized to placebo. Hypomagnesemia was reported in one patient (11005 and 03002) in each treatment arm. Hematuria was reported for one patient (12002) in the placebo group. Hypokalemia was detected in three patients (10001, 10007, 06002) receiving torsemide but none randomized to placebo[16].

SUMMARY

This was a multicenter, randomized, placebo controlled, parallel, double-blind study, in patients with chronic renal dysfunction[17]. The degree of renal dysfunction was assessed by an estimated creatinine clearance in sixty-one (89.7%) patients.

This clinical trial was performed in three phases: a torsemide dose titration phase, a torsemide treatment phase, and a random-off treatment period during which only patients who had responded to torsemide treatment were assigned randomly to either continue torsemide at a stable dose or switch to placebo. Each phase was approximately 4 weeks in duration. Torsemide was titrated up to 200 mg QD or BID to produce "an optimal therapeutic state regarding body weight and edema." Thirty-four patients, males and females, were randomized to torsemide or placebo during the random-off treatment period.

Patients' demographics were well-balanced between the groups. Overall, however the patient population studied was not representative of the US population with CRI, since the attributed etiology of CRI was hypertension in over 80% of the patients. As previously discussed, at least 44.1% of the patients randomized to either group had normal serum creatinine values at baseline and probably none or mild renal dysfunction.

The primary endpoint was the change in body weight from baseline to the last visit of the random-off period, based on measurements taken in the clinic, i.e., "peak" diuretic effect. In this study, of a patient population composed of known responders to torsemide mainly with "hypertensive nephropathy", patients who received placebo during the random-off treatment period showed a significantly greater mean increase in body weight at endpoint than did patients who remained on torsemide. This torsemide effect was significantly different from placebo at "trough" (1.69 lb. difference, $p<0.05$) as well as at "peak" (3.09 lb. difference, $p<0.001$). Although, the study was not powered to carry out subgroup analyses, degree of renal dysfunction, as assessed by serum creatinine levels at baseline may determine the magnitude of the diuretic response to torsemide (Figure 8a).

With respect to changes in the signs of fluid retention, i.e., peripheral edema, the clinical capacity of being able to determine a change in edema status for individual patients from none, to barely depressed, to 2mm, etc., is doubted.

The safety profile of torsemide in patients with CRI based on this study, with the caveat of being small and of short duration, resembles what is already known about its side effects.

Of note, pharmacokinetic studies of torsemide in chronic renal insufficiency, MF 8212 and 8213, submitted in the original NDA support the use of the diuretic up to 200 mg QD in this patient population.

Juan Carlos Pelayo, M.D.

[16] According to the sponsor, fourteen patients had serum potassium levels within the range of 3.0-3.4 mEq/L, after visit one, while treated with torsemide. Potassium supplements were initiated or re-instituted after serum potassium levels fell below normal (NDA 20136, Volume 1, page 69).

[17] If this supplemental application for torsemide is approved, the sought modification of the labeling by the sponsor should actually read ..."to be effective in the treatment of weight gain associated with chronic renal failure".

CC:

Orig. to HFD-110, NDA 20136
HFD-110 / CSO / J.C. Pelayo / S.T. Chen / D. Throckmorton

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20136/S009 and 20137/S008

CHEMISTRY REVIEW(S)

SEP 3 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-136 / S-009 (tablets) Review #2 REVIEW DATE: Sept 2, 1997
20-137 / S-008 (injection)

Submission Type	Document Date	CDER Date	Content / Topics Covered
Supplement Amends			Final printed labeling for efficacy supplements - treatment of edema associated with chronic renal failure
Tablets	Aug 15, 1997	Aug 18, 1997	
Injection	Aug 15, 1997	Aug 18, 1997	

NAME & ADDRESS OF APPLICANT:
Boehringer Mannheim Corporation
101 Orchard Ridge Drive
Gaithersburg, Maryland 20878

DRUG PRODUCT NAME
Trade Names: Demadex® (torsemide) Tablets and Demadex® (torsemide) Ampuls
Nonproprietary /USAN: torsemide Code Name : BM 02.015
Chemical Name: 1-isopropyl-3-[(4-m-toluidino-3-pyridyl)sulfonyl]urea
Chemical Class: diuretic in the pyridine-sulfonylurea class

SUPPLEMENTS PROVIDE FOR: New indication, i.e., treatment of edema due to chronic renal failure

PHARMACOL. CATEGORY / INDICATION:
1) Prior to these supplements: Management of edema due to congestive heart failure, renal failure, cirrhosis and hypertension
2) These efficacy supplements: Treatment of edema associated with chronic renal failure

DOSAGE FORM: Oral Tablet STRENGTHS: 5 mg, 10 mg, 20 mg and 100 mg
Injection, sterile solution 10 mg/mL

DISPENSED: Rx

SUPPORTING DOCUMENTS:
1) T-Con record in RJW Log Book between RJ Wolters and Ms. Peterson on February 20, 1997
2) Approvable Letter dated April 11, 1997 to 20-136/S-009 dated May 3, 1996
3) Amendments dated March 25, 1997 and April 21, 1997
4) T-Con between Gary Buehler and Ms Peterson on July 3, 1997

REMARKS/COMMENTS: A single Package Insert applies to both dosage forms. The Description and How Supplied sections were examined in general and for conformity with Dr. Wolters' discussion with Ms. Peterson on Feb 20, 1997

CONCLUSIONS & RECOMMENDATIONS: Recommend approval of both supplements

Florian Zielinski Sept 2, 1997
Florian W. Zielinski, Review Chemist

9/31/97

Distribution:
Orig. NDA 20-136 S-009
Orig.: NDA 20-137 S-008
HFD-110 Division File
HFD-110 Florian Zielinski
HFD-110 CSO, Gary Buehler
Initialed by: RJ Wolters
File names: NDA 20137 S-008, FPL
and NDA 20136 S-009, FPL

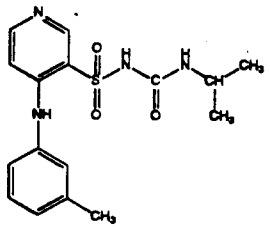
APR 3 1997

CHEMIST'S REVIEW OF SUPPLEMENT

1. ORGANIZATION: HFD-110
2. NDA NUMBER: **20-137**
4. SUPPLEMENT NUMBER/DATE: **SE2-008**/05-03-96
5. AMENDMENTS/REPORTS/DATES: 03-25-97
6. REC'D BY CHEMIST: 04-01-97

7. APPLICANT NAME AND ADDRESS:
Boehringer Mannheim Corporation
Therapeutics Division
101 Orchard Ridge Drive
Gaithersburg, MD 20878

8. NAME OF DRUG: Demadex Injection
9. NONPROPRIETARY NAME: torsemide
10. CHEMICAL NAME/STRUCTURE: 1-isopropyl-3-[(4-*m*-toluidino-3-pyridyl)sulfonyl]urea



11. DOSAGE FORMS: SVS
12. POTENCY: 10 mg/mL
13. PHARM. CATEGORY:
14. HOW DISPENSED: RX
15. RECORDS AND REPORTS:
CURRENT: YES
16. RELATED IND/NDA/DMF(S):
17. SUPPLEMENT PROVIDES FOR: a labeling change to allow for long term use of Demadex in patients with chronic renal insufficiency.
18. COMMENTS: The labeling change is apparently intended for the tablet form, but since the ampuls and tablets share their labeling this information is also being submitted to the NDA for the Demadex Injection. This amendment updates the EA originally provided with the NDA to consider the potential for expanded use of Demadex as a result of the labeling change. The only change in the EA is a revision of the estimated fifth year production volume of Demadex tablets from This results in a calculated EIC of This is well below the Tier 0 threshold, and consequently will not alter the original conclusion of the NDA EA review which resulted in the issuance of a FONSI.

19. CONCLUSIONS AND RECOMMENDATIONS: Recommend that this supplement is approvable from a CMC standpoint.

20. REVIEWER:
NAME: Christopher S. Coughlin, Ph.D.

SIGNATURE: 4-1-97
DATE COMPLETED: 04-01-97

copies:
HFD-110 ORIG NDA
DIV FILE
C. Coughlin
CSO
INIT: R. Wolters_____date 4/3/97

File: Coughlin HD:Documents:1997:SUPP:20-137/S-008 rev.1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20136/S009 and 20137/S008

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/ODE-I/DIV CARDIO-RENAL DRUGS

Date: 04/09/97

From: Shaw T. Chen, M.D., Ph.D., Medical Group Leader, HFD-110
To: Director, Division of Cardiorenal Drug Products, HFD-110

SUBJECT: NDA 20-136/SE2-009, Tablets
NDA 20-137/SE2-008, Injections
Demadex (torsemide) for edema in chronic renal failure, Approvability

BACKGROUND

This memorandum and the attached material constitute the Team Leader's recommendation that Demadex be approved for chronic use in renal failure.

Torsemide is a loop diuretic previously approved for hypertension and the following indication:

> *"...treatment of edema associated with congestive heart failure, renal disease or hepatic disease."*

but long-term use was not recommended with the following disclaimer in labeling (indication):

> *"Chronic use of any diuretic in renal or hepatic disease has not been studied in adequate and well-controlled trials".*

While there was little doubt that torsemide, regardless of formulation, is a potent acute diuretic in non-anuric patients with renal failure*, data in the original NDA submission were not convincing to support any claim of clinical benefit for chronic use in renal failure (see Dr. Rodin's and Dr. Fenichel's reviews). Among the 15 studies** in renal failure included in the original NDA, 7 were single dose (oral or i.v.), 1 was a 3-day iv study and 7 of the 8 two-four week studies were not well controlled (vs furosemide, no concurrent placebo). In the only multiple dose (12 weeks) and placebo-controlled trial (Study MF 3917) of decent size (103 hemodialysis patients), torsemide at 200 mg daily was not distinguishable from placebo in interdialysis weight gain (no other clinical endpoints were measured), a finding deemed very convincing by Drs. Rodin and Fenichel.

The sponsor now submitted additional information to show that in patients with chronic renal insufficiency, torsemide is effective in preventing fluid re-accumulation when administered over a period of time long enough to achieve a steady state in fluid balance. The clinical data submitted with these supplements have been reviewed in details by Dr. Pelayo. Results of the new study are reasonably convincing to support chronic use of torsemide in renal failure, but reconciliation with previous data must be incorporated into the labeling. We did not request verification of statistics by our biometric staff and there are no other pending regulatory issues to be resolved prior to approval of this application.

* Based on single dose, baseline- and furosemide controlled studies.

** Two of 15 were considered by Dr. Rodin as too small and seriously flawed.

THE NEW CLAIM

The sponsor proposed the following change in indication:

> "Demadex (torsemide) is indicated treatment of edema associated with congestive heart failure, renal disease or hepatic disease. *Chronic use of torsemide has been found to be effective in the treatment of edema associated with renal failure.*"

with the above limitation on long-term use modified to concern only the hepatic disease:

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

STUDY PROTOCOL & EXECUTION

As described in Dr. Pelayo's primary review, Study MF8264 was a multicenter, randomized, double-blind, parallel placebo controlled study in patients with stable chronic renal insufficiency. After a three-week dose titration (up to 200 mg bid) and a 4-week maintenance treatment phase for all patients, torsemide was compared with placebo in an additional 4- week* double-blind, randomized withdrawal phase.

The primary endpoint was change in body weight (measured at clinic visits) over the period of randomized withdrawal phase. Various clinical and laboratory parameters were specified as secondary endpoints (see Page 5 of Dr. Pelayo's review). The protocol planned to admit approximately 30 patients per treatment group.

Patient demographic and other characteristics were well-matched in the two treatment groups. It should be emphasized that, unlike those in the previous long-term and controlled study (MF3917, see above), patients in this study were not dialysis-dependent. Creatinine clearance must be $\leq$ 60 ml/min, but not all have actual measurements. Instead, values estimated from serum creatinine and Cockcroft-Gault formula were acceptable. While by entry criteria, all patients must have edema or must be receiving stable doses of furosemide or bumetanide, the reviewers had some doubt about the degree of renal insufficiency in patients with normal serum creatinine but no actual measurement of creatinine clearance. In this study, creatinine clearance was actually measured in only 10% of patients and 44% of patients in either treatment group had serum creatinine within the normal range (see Table 5 of primary review)**. Frequency of medications commonly used in renal failure (Table 7, ibid) and profile of metabolic derangements (Table 8, ibid) also suggested that renal insufficiency in this group of patients was only of mild degree.

In terms of etiologies of renal failure, the patient group in this study are somewhat different from other end-stage renal disease (ESRD) population in general (more of hypertension in the former, see Page 8 of primary review). However, there is no reason to suspect that the pharmacological activities of torsemide would be significantly different in patients of other underlying diseases.

Other than the above concerns, the study was well designed and conducted.

* Patients who entered the last phase of the study but could not tolerate the withdrawal for various reasons and were discontinued from the study before the end of 4-week were considered "early completers".

** It is still possible, though not as common, that normal serum creatinine can give a low clearance estimated by the Cockcroft-Gault formula. For all patients, creatinine clearance ranged 15-64 ml/min (Table 3, ibid).

EFFICACY RESULTS

Of the 82 patient enrolled, 68 completed the titration and maintenance treatment phase and were randomized evenly to either continue on torsemide or withdrawal to placebo. After 7 weeks of torsemide treatment (including dose titration), patients continued on torsemide had significantly less weight gain than that of those switched to placebo over the next 4-week randomized withdrawal period:

	Torsemide	placebo	p-value
center-adjusted mean increase	0.46 lbs	3.55 lbs	<0.001

The 95% confidence interval of the between group difference was from 1.87 lbs to 4.32 lbs. The differential in weight gain was evident by the third day after randomization (Figure 4, primary review). With the exception that women may have a better response to torsemide than men, this treatment difference was independent of age, race and creatinine clearance at screening. However, the sample size was too small to allow any meaningful subgroup comparison. The same limitation applies to the analysis on serum creatinine, although the data suggested treatment effect was probably more pronounced in patients with normal serum creatinine (Page 17 of primary review). As more torsemide patients completed the study (30 vs 14 in placebo), the intent-to-treat analysis with carry-forward body weights probably underestimated the advantage of torsemide had all patients been weighed at the end of randomized withdrawal period.

Patient-recorded body weight gains, a secondary endpoint and a "trough" drug effect (Figure 9 of primary review), were well-correlated with the primary finding (2.00 lbs for placebo vs 0.31 lb for torsemide). The difference in mean number of days patients remained in the randomized treatment (15.9 days for placebo vs 26.4 days for torsemide, Figure 11, ibid.) suggested that continuing on torsemide was more tolerable than switching to placebo. Changes in peripheral edema also favored torsemide, with more active-treatment patient maintained or improved their status and less worsened as compared with placebo (Figure 10, ibid). This was consistent with the fact that more placebo (than torsemide) patients who developed >3mm depressed peripheral edema:

% of patients	Placebo		Torsemide	
edema status	baseline	endpoint	baseline	endpoint
≥ 3 mm depressed	2.9%	29.4%	2.9%	5.8%

However, more than 80% of patients had no or little edema (barely depressable) at baseline and the assessment of treatment effect required one to differentiate 1-2 mm depression for edema. Results of other secondary endpoints, i.e., signs/symptoms of fluid retention (peripheral edema, rales, paroxysmal nocturnal dyspnea and orthopnea), were not impressive (Tables 12-17 of NDA study report, see also Pages 18-20 of primary review).

SAFETY EXPERIENCES

All 82 enrolled patients were included in the safety analyses. Greater than 90% of patients were treated with open label torsemide for at least 4 weeks and of those entered the randomized withdrawal period, more than 70% completed the 4 week course (Tables 14 and 15 of primary review). In general, there were no surprising safety issues with chronic use (i.e. up to 12 weeks) of torsemide which would require modification of the related section in the current labeling. However, it should be kept in mind that total sample size and frequency of individual adverse events were too small to justify any formal analysis and duration of exposure was not truly long-term (comparative experiences of only 4 weeks).

As expected from previous experience, most common adverse events were hypokalemia (8.8% vs 0% for placebo) and dizziness (5.9% vs 0% for placebo). While baseline potassium levels and changes at the end of double-blind period were not distinguishable between treatment groups (Table 12 of primary review), more torsemide treated patients were receiving potassium supplement (12 vs 3 in placebo). Profile of serious adverse experiences and scope of reasons for withdrawal due to adverse events or dose-reduction in study drug, as well as abnormal laboratory findings were all within the range described in the original NDA or not unexpected from underlying medical conditions (see Page 22 of primary review). One death in torsemide treated patients was reported, but was most likely not drug related (see also Page 22, ibid).

CONCLUSION & RECOMMENDATION

The results of this study have demonstrated that after 4-8 weeks of torsemide treatment, patients in mild renal failure who continued on torsemide clearly had less weight gains than those who were randomly withdrawn to placebo. This finding on office visit body weight was consistent with the patients' own measurements in weight changes and correlated with the fact that more torsemide patients tolerated the randomized withdrawal for longer period of time. The effect of torsemide on peripheral edema also supported the efficacy claim, although the method of assessment (e.g., 3 mm depression) was somewhat tenuous and changes in other symptomatic parameters were less impressive.

However, as emphasized by Dr. Pelayo in his review, patient population in this study were of less severe renal dysfunction who had near normal serum creatinine and did not require dialysis. This issue was confounded by the reviewers' legitimate reservation about the accuracy of renal function assessment in this study (see Protocol above). While the creatinine clearance must be 60 ml/min or less for patients to be enrolled, only 10% of patients had actual measurements (the rest estimated from serum creatinine). In patients with more severe renal failure, such as those on hemodialysis in Study 3917 (see above in Background), torsemide was clearly (and convincingly) not effective. This latter observation was also consistent with the subgroup finding in the new study suggesting that, although not a robust analysis, torsemide may be more effective in patients with normal serum creatinine (than with higher serum creatinine). Thus, the claim of efficacy for chronic use of torsemide in renal failure can only apply to patients with mild degree of renal insufficiency. In the labeling, the patient population to be treated should be restricted as follows:

Chronic use of torsemide has been found to be effective in the treatment of edema associated with *non-dialysis dependent* renal failure."

Based on the results of this new study and data submitted with the initial NDA (Studies MF8212 and MF8213, see Dr. Rodin's review), the same new claim may be extended to the intravenous formulation (to be administered as 30-min injections) without additional studies.

cc:
ORIG: NDA- 20-136, 20-137
HFD-110
HFD-110/Buehler, Pelayo
HFD-110/SChen/04/09/97

Shaw T. Chen, M.D.,Ph.D.

SEP 9 1997

LABELING REVIEW

NDA 20-136/S-009 Demadex (torsemide) Tablets
NDA 20-137/S-008 Demadex (torsemide) Injection

Sponsor: Boehringer Mannheim Corporation
Therapeutics
101 Orchard Drive
Gaithersburg, MD 20878

Date of Original Submissions: May 3, 1996
Date of Approvable Letter: April 11, 1997
Date of FPL Submission: August 15, 1997

BACKGROUND

The supplemental applications provide for use of Demadex Tablets and Injection for the treatment of edema associated with chronic renal failure.

A marked-up draft (appended to this review)of the affected sections of the labeling was sent to the firm with the approvable letter. The submitted FPL conformed to this draft. In addition, in a July 3, 1997 telephone conversation between Ms. Jayne Peterson and myself, it was agreed that the sentence under the CLINICAL PHARMACOLOGY heading, Paragraph 13 stating

could be deleted. This sentence was deleted under Indications and Usage and Dosage and Administration, and it was considered an oversight that it was not deleted under Clinical Pharmacology.

Ms. Peterson also discussed changes under the HOW SUPPLIED section relating to the manufacture and distribution of the two Demadex dosage forms. The following text was agreed to and appears in the FPL:

> Tablets manufactured by
> Boehringer Mannheim, GmbH, Mannheim, Germany
>
> Tablets and Ampuls Distributed by
> Boehringer Mannheim Corporation, Therapeutics Division, Gaithersburg, MD 20878

The labeling was reviewed and found to be acceptable. An approval letter will be drafted for Dr. Lipicky's signature.

Gary Buehler 9/9/97
Gary Buehler
Project Manager

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton
HF-2 MEDWATCH

SEP 9 1997

EXCLUSIVITY SUMMARY for NDA # 20-136/20-137 SUPPL # S-009/S-008

Trade Name Demadex Tablets Demadex Inj Generic Name Torsemide

Applicant Name Boehringer Mannheim HFD- 110

Approval Date 9/9/97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE-2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) **Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?**

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) **If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:**

Investigation #1, Study # MF 8264

Investigation #2, Study # MF 3917

Investigation #3, Study # _____

In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) **For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")**

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /X/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 20-137 Study # MF3917
NDA # _____ Study # _____
NDA # _____ Study # _____

b) **For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?**

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /X/	NO /[redacted]/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # 20-137 Study # MF3917
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # MF 8264

Investigation #__, Study # [redacted]

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /X/ NO /___/ Explain: _____

Investigation #2

IND # YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

NA

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

_____

Gary Buehler
Signature
Title: Project Manager

9/9/97
Date

Ray Lipicky
Signature of Division Director

9/19/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

8/8/95

101 Orchard Ridge Drive
Gaithersburg, MD 20878
USA

Fax: +1 (301) 990 3825 (Sales)

DESK COPY

BOEHRINGER MANNHEIM CORPORATION

Mr. Gary Buehler

Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Document Control Room, HFD-110
5600 Fishers Lane
Rockville, MD 20857

March 25, 1997

Re: DEMADEX® (Torsemide) Tablets and Ampuls
NDA No. 20-136/S-009 and
NDA No. 20-137/S-008
Amendment to a Pending Application

Dear Dr. Lipicky:

Reference is made to the Demadex® (torsemide) tablet NDA 20-136/S-009 dated May 3, 1996 and the Demadex® (torsemide) ampul NDA 20-137/S-008 dated May 3, 1996 requesting a labeling change to allow for the long-term use of Demadex® in patients with chronic renal insufficiency.

Reference is also made to a February 24, 1997 request from Mr. Gary Buehler of your Division for revised data to the Environmental Assessment (EA) submitted in the original filing of the Demadex® tablet NDA 20-136 on March 28, 1991. This request was made in consideration of the potential for expanded use of Demadex® tablets as a result of approval of the above noted Supplemental New Drug Applications. At this time we are providing the requested data (attached).

Boehringer Mannheim Corporation, Therapeutics Division certifies that a copy of this Amendment is being submitted to our local district FDA office in Baltimore, Maryland.

If you have any further questions regarding this submission, please do not hesitate to contact Ms. Jayne E. Peterson, Manager, Regulatory Affairs at (301) 216-3800.

Sincerely,

Claes Helmers, M.D., Ph.D.
Vice President, Medical and Scientific Affairs
and Interim Head, Regulatory Affairs and Quality Operations

JEP/kmr

Attachment

cc: Mr. Gary Buehler (Desk Copy)
Baltimore District Office

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905 AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Boehringer Mannheim Corporation, Therapeutics Division	3/25/97
ADDRESS *(Number, Street, City, State and ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
101 Orchard Ridge Drive Gaithersburg, MD 20878	301-216-3800
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
	20-136

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
torsemide	DEMADEX

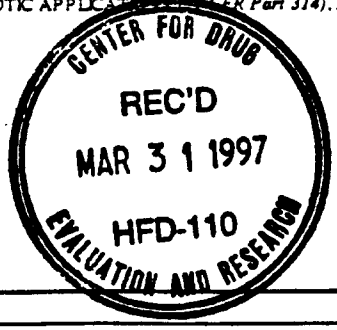
CODE NAME *(If any)*	CHEMICAL NAME
BM 02.015	1-isopropyl-3-[(4-m-toluidino-3-pyridyl) sufonyl] urea

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS(S)
Tablets	Oral	5mg, 10mg, 20mg, 100mg

PROPOSED INDICATIONS FOR USE

Edema due to congestive heart failure, renal failure, cirrhosis and hypertension

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))*: _____

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*