DEMADEX®

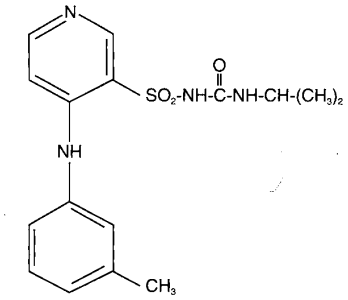
(torsemide)

TABLETS

IN-0455-0X Rev. 08/12

DESCRIPTION

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



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

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

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 DEMADEX tablets is approximately 80%, with little intersubject variation; the 90% confidence interval is 75% to 89%. The drug is absorbed with little first-pass metabolism, and the serum concentration reaches its peak (C_{max}) within 1 hour after oral administration. C_{max} and area under the serum concentration-time curve (AUC) after oral administration are proportional to dose over the range of 2.5 mg to 200 mg.

Simultaneous food intake delays the time to C_{max} by about 30 minutes, but overall bioavailability (AUC) and diuretic activity are unchanged. Absorption is essentially unaffected by renal or hepatic dysfunction.

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

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

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

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

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

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

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

Clinical Effects

With oral dosing, the onset of diuresis occurs within 1 hour and the peak effect occurs during the first or second hour and 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

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

When DEMADEX 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 DEMADEX is suddenly

stopped, blood pressure returns to pretreatment levels over several days, without overshoot.

DEMADEX 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

DEMADEX is 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.

DEMADEX is indicated for the treatment of hypertension alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

DEMADEX is contraindicated in patients with known hypersensitivity to DEMADEX or to sulfonylureas.

DEMADEX is contraindicated in patients who are anuric.

WARNINGS

Hepatic Disease With Cirrhosis and Ascites

DEMADEX 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 DEMADEX (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 DEMADEX.

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 DEMADEX. It is not certain that these events were attributable to DEMADEX. 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, DEMADEX should be discontinued until the situation is corrected; DEMADEX may be restarted at a lower dose.

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

PRECAUTIONS

Laboratory Values

Potassium: See WARNINGS.

Calcium

Single doses of DEMADEX 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 DEMADEX for an average of 11 months, hypocalcemia was not reported as an adverse event.

Magnesium

Single doses of DEMADEX 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 DEMADEX 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 DEMADEX 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 DEMADEX, respectively.

Blood Urea Nitrogen (BUN), Creatinine and Uric Acid

DEMADEX produces small dose-related increases in each of these laboratory values. In hypertensive patients who received 10 mg of DEMADEX 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 DEMADEX, but its incidence has been similar to that seen in patients receiving placebo.

Glucose

Hypertensive patients who received 10 mg of daily DEMADEX 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 DEMADEX 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 DEMADEX 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 DEMADEX daily, no clinically significant differences from baseline lipid values were observed after 1 year of therapy.

Other

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

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

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

The natriuretic effect of DEMADEX (like that of many other diuretics) is partially inhibited by the concomitant administration of indomethacin. This effect has been demonstrated for DEMADEX 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 DEMADEX 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 DEMADEX and cholestyramine are used concomitantly, simultaneous administration is not recommended.

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

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 DEMADEX 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 DEMADEX have not been studied.

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

Pregnancy

Pregnancy Category B.

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

Labor and Delivery

The effect of DEMADEX on labor and delivery is unknown.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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

Geriatric Use

Of the total number of patients who received DEMADEX 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

To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at 1-800-526-3840 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

The reported side effects of DEMADEX 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 DEMADEX 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 DEMADEX and 3.4% (13/380) with furosemide in patients with congestive heart failure, 2.0% (8/409) with DEMADEX and 4.8% (11/230) with furosemide in patients with renal insufficiency, and 7.6% (13/170) with DEMADEX and 0% (0/33) with furosemide in patients with cirrhosis.

The most common reasons for discontinuation of therapy with DEMADEX 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 DEMADEX are shown in Table 1.

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

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

The daily doses of DEMADEX 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 DEMADEX 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 DEMADEX, 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 DEMADEX 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 DEMADEX 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 DEMADEX 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 DEMADEX. One patient in the group treated with DEMADEX withdrew due to myalgia, and one in the placebo group withdrew due to gout.

Hypokalemia: See WARNINGS.

Postmarketing Experience

The following adverse reactions have been identified during the post approval use of Demadex. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions reported include the following: leucopenia, thrombocytopenia.

Serious skin reactions (*i.e.*, Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported in association with torsemide use.

Pancreatitis has been reported in association with torsemide use.

OVERDOSAGE

There is no human experience with overdoses of DEMADEX, 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

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

Congestive Heart Failure

The usual initial dose is 10 mg or 20 mg of once-daily oral DEMADEX. 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 DEMADEX is 20 mg of once-daily oral DEMADEX. 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 DEMADEX, 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

DEMADEX for oral administration is available as white, scored tablets containing 5 mg, 10 mg, 20 mg, or 100 mg of torsemide. The tablets are supplied in bottles of 100 as follows:

Dose	Shape	Bottle
5 mg	elliptical	NDC 0037-5005-01
10 mg	elliptical	NDC 0037-5010-01
20 mg	elliptical	NDC 0037-5020-01
100 mg	capsule shaped	NDC 0037-5001-01

Each tablet is debossed on the scored side with the logo BM and 102, 103, 104, or 105 (for 5 mg, 10 mg, 20 mg, or 100 mg, respectively). On the opposite side, the tablet is debossed with 5, 10, 20, or 100 to indicate the dose.

Storage

Store at 15° to 30°C (59° to 86°F).

R_X Only

Manufactured By: Roche Farma S.A., Leganes, Spain
For: Meda Pharmaceuticals

Meda Pharmaceuticals Inc.
Somerset, NJ 08873-4120

To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at 1-800-526-3840 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Printed in USA

IN-0455-0X Rev. 08/12