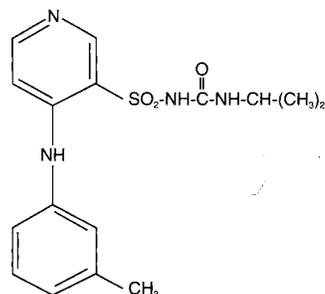


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DEMADEX[®]
(torsemide)
TABLETS
IN-0455-0X Rev. 08/12

6 **DESCRIPTION**

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



10
11 Its empirical formula is C₁₆H₂₀N₄O₃S, its pKa is 7.1, and its molecular weight is 348.43.

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

15 **CLINICAL PHARMACOLOGY**

16 **Mechanism of Action**

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

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

25 **Pharmacokinetics and Metabolism**

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

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

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

37 In normal subjects the elimination half-life of torsemide is approximately 3.5 hours.
38 Torsemide is cleared from the circulation by both hepatic metabolism (approximately
39 80% of total clearance) and excretion into the urine (approximately 20% of total
40 clearance in patients with normal renal function). The major metabolite in humans is the
41 carboxylic acid derivative, which is biologically inactive. Two of the lesser metabolites
42 possess some diuretic activity, but for practical purposes metabolism terminates the
43 action of the drug.

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

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

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

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

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

67 **Clinical Effects**

68 With oral dosing, the onset of diuresis occurs within 1 hour and the peak effect occurs
69 during the first or second hour and diuresis lasts about 6 to 8 hours. In healthy subjects
70 given single doses, the dose-response relationship for sodium excretion is linear over the
71 dose range of 2.5 mg to 20 mg. The increase in potassium excretion is negligible after a

72 single dose of up to 10 mg and only slight (5 mEq to 15 mEq) after a single dose of 20
73 mg.

74 Congestive Heart Failure

75 DEMADEx has been studied in controlled trials in patients with New York Heart
76 Association Class II to Class IV congestive heart failure. Patients who received 10 mg to
77 20 mg of daily DEMADEx in these studies achieved significantly greater reductions in
78 weight and edema than did patients who received placebo.

79 Nonanuric Renal Failure

80 In single-dose studies in patients with nonanuric renal failure, high doses of DEMADEx
81 (20 mg to 200 mg) caused marked increases in water and sodium excretion. In patients
82 with nonanuric renal failure, severe enough to require hemodialysis, chronic treatment
83 with up to 200 mg of daily DEMADEx has not been shown to change steady-state fluid
84 retention. When patients in a study of acute renal failure received total daily doses of 520
85 mg to 1200 mg of DEMADEx, 19% experienced seizures. Ninety-six patients were
86 treated in this study; 6/32 treated with torsemide experienced seizures, 6/32 treated with
87 comparably high doses of furosemide experienced seizures, and 1/32 treated with placebo
88 experienced a seizure.

89 Hepatic Cirrhosis

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

99 Essential Hypertension

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

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

108 When DEMADEx is first administered, daily urinary sodium excretion increases for at
109 least a week. With chronic administration, however, daily sodium loss comes into
110 balance with dietary sodium intake. If the administration of DEMADEx is suddenly

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

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

116 **INDICATIONS AND USAGE**

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

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

123 **CONTRAINDICATIONS**

124 DEMADEx is contraindicated in patients with known hypersensitivity to DEMADEx or
125 to sulfonylureas.

126 DEMADEx is contraindicated in patients who are anuric.

127 **WARNINGS**

128 **Hepatic Disease With Cirrhosis and Ascites**

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

134 **Ototoxicity**

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

139 **Volume and Electrolyte Depletion**

140 Patients receiving diuretics should be observed for clinical evidence of electrolyte
141 imbalance, hypovolemia, or prerenal azotemia. Symptoms of these disturbances may
142 include one or more of the following: dryness of the mouth, thirst, weakness, lethargy,
143 drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria,
144 tachycardia, nausea, and vomiting. Excessive diuresis may cause dehydration, blood-
145 volume reduction, and possibly thrombosis and embolism, especially in elderly patients.
146 In patients who develop fluid and electrolyte imbalances, hypovolemia, or prerenal
147 azotemia, the observed laboratory changes may include hyper- or hyponatremia, hyper-
148 or hypochloremia, hyper- or hypokalemia, acid-base abnormalities, and increased blood

149 urea nitrogen (BUN). If any of these occur, DEMADDEX should be discontinued until the
150 situation is corrected; DEMADDEX may be restarted at a lower dose.

151 In controlled studies in the United States, DEMADDEX was administered to hypertensive
152 patients at doses of 5 mg or 10 mg daily. After 6 weeks at these doses, the mean decrease
153 in serum potassium was approximately 0.1 mEq/L. The percentage of patients who had a
154 serum potassium level below 3.5 mEq/L at any time during the studies was essentially the
155 same in patients who received DEMADDEX (1.5%) as in those who received placebo
156 (3%). In patients followed for 1 year, there was no further change in mean serum
157 potassium levels. In patients with congestive heart failure, hepatic cirrhosis, or renal
158 disease treated with DEMADDEX at doses higher than those studied in United States
159 antihypertensive trials, hypokalemia was observed with greater frequency, in a dose-
160 related manner.

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

166 Periodic monitoring of serum potassium and other electrolytes is advised in patients
167 treated with DEMADDEX.

168 **PRECAUTIONS**

169 **Laboratory Values**

170 Potassium: See WARNINGS.

171 Calcium

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

178 Magnesium

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

185 In a long-term clinical study of DEMADDEX in patients with congestive heart failure, the
186 estimated annual change in serum magnesium was an increase of 0.2 mg/dL (0.08
187 mmol/L), but these data are confounded by the fact that many of these patients received

188 magnesium supplements. In a 4-week study in which magnesium supplementation was
189 not given, the rate of occurrence of serum magnesium levels below 1.7 mg/dL (0.70
190 mmol/L) was 6% and 9% in the groups receiving 5 mg and 10 mg of DEMADEx,
191 respectively.

192 Blood Urea Nitrogen (BUN), Creatinine and Uric Acid

193 DEMADEx produces small dose-related increases in each of these laboratory values. In
194 hypertensive patients who received 10 mg of DEMADEx daily for 6 weeks, the mean
195 increase in blood urea nitrogen was 1.8 mg/dL (0.6 mmol/L), the mean increase in serum
196 creatinine was 0.05 mg/dL (4 mmol/L), and the mean increase in serum uric acid was 1.2
197 mg/dL (70 mmol/L). Little further change occurred with long-term treatment, and all
198 changes reversed when treatment was discontinued.

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

201 Glucose

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

207 Serum Lipids

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

212 In the same short-term hypertension studies, daily doses of 5 mg, 10 mg and 20 mg of
213 DEMADEx were associated with mean increases in plasma triglycerides of 16, 13 and
214 71 mg/dL (0.15 to 0.80 mmol/L), respectively.

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

217 Other

218 In long-term studies in hypertensive patients, DEMADEx has been associated with small
219 mean decreases in hemoglobin, hematocrit, and erythrocyte count and small mean
220 increases in white blood cell count, platelet count, and serum alkaline phosphatase.
221 Although statistically significant, all of these changes were medically inconsequential.
222 No significant trends have been observed in any liver enzyme tests other than alkaline
223 phosphatase.

224 **Drug Interactions**

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

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

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

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

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

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

254 Coadministration of probenecid reduces secretion of DEMADDEX into the proximal
255 tubule and thereby decreases the diuretic activity of DEMADDEX.

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

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

262 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

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

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

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

282 **Pregnancy**

283 **Pregnancy Category B.**

284 There was no fetotoxicity or teratogenicity in rats treated with up to 5 mg/kg/day of
285 torsemide (on a mg/kg basis, this is 15 times a human dose of 20 mg/day; on a mg/m²
286 basis, the animal dose is 10 times the human dose), or in rabbits, treated with 1.6
287 mg/kg/day (on a mg/kg basis, 5 times the human dose of 20 mg/kg/day; on a mg/m²
288 basis, 1.7 times this dose). Fetal and maternal toxicity (decrease in average body weight,
289 increase in fetal resorption and delayed fetal ossification) occurred in rabbits and rats
290 given doses 4 (rabbits) and 5 (rats) times larger. Adequate and well-controlled studies
291 have not been carried out in pregnant women. Because animal reproduction studies are
292 not always predictive of human response, this drug should be used during pregnancy only
293 if clearly needed.

294 **Labor and Delivery**

295 The effect of DEMADEx on labor and delivery is unknown.

296 **Nursing Mothers**

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

300 **Pediatric Use**

301 Safety and effectiveness in pediatric patients have not been established.

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

311 **Geriatric Use**

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

316 **ADVERSE REACTIONS**

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

319 At the time of approval, DEMADEx had been evaluated for safety in approximately
320 4000 subjects: over 800 of these subjects received DEMADEx for at least 6 months, and
321 over 380 were treated for more than 1 year. Among these subjects were 564 who received
322 DEMADEx during United States-based trials in which 274 other subjects received
323 placebo.

324 The reported side effects of DEMADEx were generally transient, and there was no
325 relationship between side effects and age, sex, race, or duration of therapy.
326 Discontinuation of therapy due to side effects occurred in 3.5% of United States patients
327 treated with DEMADEx and in 4.4% of patients treated with placebo. In studies
328 conducted in the United States and Europe, discontinuation rates due to side effects were
329 3.0% (38/1250) with DEMADEx and 3.4% (13/380) with furosemide in patients with
330 congestive heart failure, 2.0% (8/409) with DEMADEx and 4.8% (11/230) with
331 furosemide in patients with renal insufficiency, and 7.6% (13/170) with DEMADEx and
332 0% (0/33) with furosemide in patients with cirrhosis.

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

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

341 **Table 1** **Reactions Possibly or Probably Drug-Related**
342 **United States Placebo-Controlled Studies Incidence**
343 **(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

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

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

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

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

368 **Hypokalemia: See WARNINGS.**

369 **Postmarketing Experience**

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

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

377 Pancreatitis has been reported in association with torsemide use.

378

379 **OVERDOSAGE**

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

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

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

390 **DOSAGE AND ADMINISTRATION**

391 **General**

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

394 **Congestive Heart Failure**

395 The usual initial dose is 10 mg or 20 mg of once-daily oral DEMADEx. If the diuretic
396 response is inadequate, the dose should be titrated upward by approximately doubling

397 until the desired diuretic response is obtained. Single doses higher than 200 mg have not
398 been adequately studied.

399 **Chronic Renal Failure**

400 The usual initial dose of DEMADDEX is 20 mg of once-daily oral DEMADDEX. If the
401 diuretic response is inadequate, the dose should be titrated upward by approximately
402 doubling until the desired diuretic response is obtained. Single doses higher than 200 mg
403 have not been adequately studied.

404 **Hepatic Cirrhosis**

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

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

412 **Hypertension**

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

417 **HOW SUPPLIED**

418 DEMADDEX for oral administration is available as white, scored tablets containing 5 mg,
419 10 mg, 20 mg, or 100 mg of torsemide. The tablets are supplied in bottles of 100 as
420 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

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

424 **Storage**

425 Store at 15° to 30°C (59° to 86°F).

426 R_x Only

427 Manufactured By: Roche Farma S.A., Leganes, Spain

428 For: Meda Pharmaceuticals

429 Meda Pharmaceuticals Inc.
430 Somerset, NJ 08873-4120

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