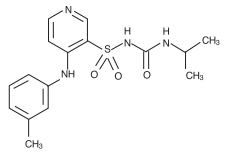
For the use only by a Registered Medical Practitioner or a Hospital or a Laboratory

TIDE INJECTION
(Torsemide Injection)

COMPOSITION
Each ml contains :
Torsemide I.P. 10 mg
Water for Injections I.P. q.s.

DESCRIPTION
Torsemide is a diuretic of the pyridine-sulfonylurea class. Its chemical name is 1-isopropyl-3-[(4-m-toluidino-3-pyridyl)sulfonyl]urea and Its empirical formula is $C_{16}H_{20}N_4O_3S$, its pKa is 7.1, and its molecular weight is 348.43 and the structural formula is :



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
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.
INDICATIONS AND USAGE
Tide injection is indicated for the treatment of oedema associated with congestive heart failure, renal or hepatic disease and essential hypertension.
CONTRAINDICATIONS
Tide injection is contraindicated in patients with known hypersensitivity to Torsemide or to sulfonylureas. It is contraindicated in patients who are anuric.
WARNINGS
FOR INTRAVENOUS INJECTION ONLY
Hepatic Disease With Cirrhosis and Ascites
Torsemide should be used with caution in patients with hepatic disease with cirrhosis and ascites, since sudden alterations of fluid and electrolyte balance may precipitate hepatic coma.
Ototoxicity
Tinnitus and hearing loss (usually reversible) have been observed after rapid intravenous injection of other loop diuretics. It is not certain that these events were attributes to Torsemide. Administered intravenously ,Torsemide should be injected slowly over 2 minutes.
Volume and Electrolyte Depletion
Patients receiving diuretics should be observed for clinical evidence of electrolyte imbalance, hypovolemia, or prerenal azotemia. Symptoms of these disturbances may include one or more of the following: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, and vomiting. Excessive diuresis may cause dehydration, blood-volume reduction, and possibly thrombosis and embolism, especially in elderly patients. In patients who develop fluid and electrolyte imbalances, hypovolemia, or prerenal azotemia, the observed laboratory changes may include hyper- or hyponatremia, hyper- or hypochloremia, hyper- or hypokalemia, acid-base abnormalities, and increased blood urea nitrogen (BUN). If any of these occur, Torsemide should be discontinued until the situation is corrected; Torsemide may be restarted at a lower dose. In controlled studies in the United States, Torsemide was administered to hypertensive patients at doses of 5 mg or 10 mg daily. After 6 weeks at these doses, the mean decrease in serum potassium was approximately 0.1 mEq/L. In patients with congestive heart failure, hepatic cirrhosis, or renal disease treated with Torsemide at doses higher than those studied in United States antihypertensive trials, hypokalemia was observed with greater frequency, in a dose-related manner. In patients with cardiovascular disease, especially those receiving digitalis glycosides, diuretic-induced hypokalemia may be a risk factor for the development of arrhythmias. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or ACTH. Periodic monitoring of serum potassium and other electrolytes is advised in patients treated with Torsemide.
PRECAUTIONS
Laboratory Values
Potassium: See WARNINGS.
Calcium
Single doses of Torsemide increased the urinary excretion of calcium by normal subjects, but serum calcium levels were slightly increased in 4 to 6 week hypertension trials. In a long-term study of patients with congestive heart failure, the average 1-year change in serum calcium was a decrease of 0.10 mg/dL (0.02 mmol/L). Among 426 patients treated with Torsemide for an average of 11 months, hypocalcemia was not reported as an adverse event.
Magnesium
Single doses of Torsemide caused healthy volunteers to increase their urinary excretion of magnesium, but serum magnesium levels were slightly increased in 4 to 6 week hypertension trials. In long-term hypertension studies, the average 1 year change in serum magnesium was an increase of 0.03 mg/dL (0.01 mmol/L). Among 426 patients treated with Torsemide for an average of 11 months, one case of hypomagnesemia (1.3 mg/dL [0.53 mmol/L]) was reported as an adverse event.
Blood Urea Nitrogen (BUN), Creatinine and Uric Acid
Torsemide produces small dose-related increases in serum creatinine, serum uric acid change occurred with long-term treatment, and all changes reversed when treatment was discontinued.
Symptomatic gout has been reported in patients receiving Torsemide, but its incidence has been similar to that seen in patients receiving placebo.
Glucose
Hypertensive patients who received 10 mg of daily Torsemide experienced a mean increase in serum glucose concentration of 5.5 mg/dL (0.3 mmol/L) after 6 weeks of therapy 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
Torsemide were associated with mean increases in the controlled short term hypertension studies.
Other
In long-term studies in hypertensive patients, Torsemide has been associated with small mean decreases in hemoglobin, hematocrit, and erythrocyte count and small mean increases in white blood cell count, platelet count, and serum alkaline phosphatase. Although statistically significant, all of these changes were medically inconsequential. No significant trends have been observed in any liver enzyme tests other than alkaline phosphatase.
DRUG INTERACTIONS
In patients with essential hypertension, Torsemide has been administered together with beta-blockers, ACE inhibitors, and calcium-channel blockers. In patients with congestive heart failure, Torsemide has been administered together with digitalis glycosides, ACE inhibitors, and organic nitrates. None of these combined uses was associated with new or unexpected adverse events. Torsemide does not affect the protein binding of glyburide or of warfarin, the anticoagulant effect of phenprocoumon (a related coumarin derivative), or the pharmacokinetics of digoxin or carvedilol (a vasodilator / beta - blocker). In healthy subjects, coadministration of Torsemide was associated with significant reduction in the renal clearance of spironolactone, with corresponding increases in the AUC. However, clinical experience indicates that dosage adjustment of either agent is not required.

Because Torsemide and salicylates compete for secretion by renal tubules, patients receiving high doses of salicylates may experience salicylate toxicity when Torsemide is concomitantly administered. Also, although possible interactions between Torsemide and nonsteroidal anti-inflammatory agents (including aspirin) have not been studied, coadministration of these agents with another loop diuretic (furosemide) has occasionally been associated with renal dysfunction. The natriuretic effect of Torsemide (like that of many other diuretics) is partially inhibited by the concomitant administration of indomethacin. This effect has been demonstrated for Torsemide under conditions of dietary sodium restriction (50 mEq/day) but not in the presence of normal sodium intake (150 mEq/day). The pharmacokinetic profile and diuretic activity of Torsemide are not altered by cimetidine or spironolactone. Coadministration of digoxin is reported to increase the area under the curve for Torsemide by 50%, but dose adjustment of Torsemide is not necessary.
Concomitant use of Torsemide and cholestyramine has not been studied in humans but, in a study in animals, coadministration of cholestyramine decreased the absorption of orally administered Torsemide. If Torsemide and cholestyramine are used concomitantly, simultaneous administration is not recommended. Coadministration of probenecid reduces secretion of Torsemide into the proximal tubule and thereby decreases the diuretic activity of Torsemide. Other diuretics are known to reduce the renal clearance of lithium, inducing a high risk of lithium toxicity, so coadministration of lithium and diuretics should be undertaken with great caution, if at all. Coadministration of lithium and Torsemide has not been studied. Other diuretics have been reported to increase the ototoxic potential of aminoglycoside antibiotics and of ethacrynic acid, especially in the presence of impaired renal function. These potential interactions with Torsemide have not been studied.
Pregnancy
Pregnancy Category B.
There was no fetotoxicity or teratogenicity in rats treated with up to 5 mg/kg/day of Torsemide (on a mg/kg basis, this is 15 times a human dose of 20 mg/day; on a mg/m^2 basis, the animal dose is 10 times the human dose), or in rabbits, treated with 1.6 mg/kg/day (on a mg/kg basis, 5 times the human dose of 20 mg/kg/day; on a mg/m^2 basis, 1.7 times this dose). Fetal and maternal toxicity (decrease in average body weight, increase in fetal resorption and delayed fetal ossification) occurred in rabbits and rats given doses 4 (rabbits) and 5 (rats) times larger. Adequate and well-controlled studies have not been carried out in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Labor and Delivery
The effect of Torsemide on labor and delivery is unknown.
Nursing Mothers
It is not known whether Torsemide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Torsemide is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Administration of another loop diuretic to severely premature infants with edema due to patent ductus arteriosus and hyaline membrane disease has occasionally been associated with renal calcifications, sometimes barely visible on X-ray but sometimes in staghorn form, filling the renal pelves. Some of these calculi have been dissolved, and hypercalciuria has been reported to have decreased, when chlorothiazide has been coadministered along with the loop diuretic. In other premature neonates with hyaline membrane disease, another loop diuretic has been reported to increase the risk of persistent patent ductus arteriosus, possibly through a prostaglandin-E-mediated process. The use of Torsemide in such patients has not been studied.
Geriatric Use
Of the total number of patients who received Torsemide in United States clinical studies, 24% were 65 or older while about 4% were 75 or older. No specific age-related differences in effectiveness or safety were observed between younger patients and elderly patients.
ADVERSE REACTIONS
At the time of approval, Torsemide had been evaluated for safety in approximately 4000 subjects: over 800 of these subjects received Torsemide for at least 6 months, and over 380 were treated for more than 1 year. Among these subjects were 564 who received Torsemide during United States-based trials in which 274 other subjects received placebo. The reported side effects of Torsemide were generally transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects occurred in 3.5% of United States patients treated with Torsemide and in 4.4% of patients treated with placebo. In studies conducted in the United States and Europe, discontinuation rates due to side effects were 3.0% (38/1250) with Torsemide and 3.4% (13/380) with furosemide in patients with congestive heart failure, 2.0% (8/409) with Torsemide and 4.8% (11/230) with furosemide in patients with renal insufficiency, and 7.6% (13/170) with Torsemide and 0% (0/33) with furosemide in patients with cirrhosis. The most common reasons for discontinuation of therapy with Torsemide were (in descending order of frequency) dizziness, headache, nausea, weakness, vomiting, hyperglycemia, excessive urination, hyperuricemia, hypokalemia, excessive thirst, hypovolemia, impotence, esophageal hemorrhage, and dyspepsia. Dropout rates for these adverse events ranged from 0.1% to 0.5%.
Asthenia, Diarrhea, ECG Abnormality, Cough Increase, Constipation, Arthralgia, Sore Throat, Myalgia, Chest Pain, Insomnia, Edema, Nervousness, atrial fibrillation, digitalis intoxication, gastrointestinal hemorrhage, hypotension, shunt thrombosis, rash, rectal bleeding, syncope, and ventricular tachycardia, Angioedema has been reported in a patient exposed to torasemide who was later found to be allergic to sulfa drugs. Arthritis, various other nonspecific musculoskeletal problems, gout have also been reported with torsemide use.
OVERDOSAGE
There is no human experience with overdoses of Torsemide, but the signs and symptoms of overdosage can be anticipated to be those of excessive pharmacologic effect: dehydration, hypovolemia, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, and hemoconcentration. Treatment of overdosage should consist of fluid and electrolyte replacement. Laboratory determinations of serum levels of Torsemide and its metabolites are not widely available. No data are available to suggest physiological maneuvers (eg, maneuvers to change the pH of the urine) that might accelerate elimination of Torsemide and its metabolites. Torsemide is not dialyzable, so hemodialysis will not accelerate elimination.
DOSAGE AND ADMINISTRATION
General
Dosage adjustment in the elderly is not necessary.
Because of the high bioavailability of Torsemide, oral and intravenous doses are therapeutically equivalent, so patients may be switched to and from the intravenous form with no change in dose. Torsemide intravenous injection should be administered either slowly as a bolus over a period of 2 minutes or administered as a continuous infusion. If Torsemide is administered through an IV line, it is recommended that, as with other IV injections, the IV line be flushed with Normal Saline (Sodium Chloride Injection, USP) before and after administration. Torsemide injection is formulated above pH 8.3. Flushing the line is recommended to avoid the potential for incompatibilities caused by differences in pH which could be indicated by color change, haziness or the formation of a precipitate in the solution.
If Torsemide is administered as a continuous infusion, stability has been demonstrated through 24 hours at room temperature in plastic containers for the following fluids and concentrations :
200 mg Torsemide (10 mg/mL) added to :
250 mL Dextrose 5% in water
250 mL 0.9% Sodium Chloride
500 mL 0.45% Sodium Chloride
50 mg Torsemide (10 mg/mL) added to:
500 mL Dextrose 5% in water
500 mL 0.9% Sodium Chloride
500 mL 0.45% Sodium Chloride
Before administration, the solution of Torsemide should be visually inspected for discoloration and particulate matter. If either is found, the ampoule should not be used.
Congestive Heart Failure
The usual initial dose is 10 mg or 20 mg of once-daily oral or intravenous Torsemide. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.
Chronic Renal Failure
The usual initial dose of Torsemide is 20 mg of once-daily oral or intravenous Torsemide. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.
Hepatic Cirrhosis
The usual initial dose is 5 mg or 10 mg of once-daily oral or intravenous Torsemide, administered together with an aldosterone antagonist or a potassium-sparing diuretic. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 40 mg have not been adequately studied. Chronic use of any diuretic in hepatic disease has not been studied in adequate and well-controlled trials.
Hypertension
The usual initial dose is 5 mg once daily. If the 5 mg dose does not provide adequate reduction in blood pressure within 4 to 6 weeks, the dose may be increased to 10 mg once daily. If the response to 10 mg is insufficient, an additional antihypertensive agent should be added to the treatment regimen.
EXPIRY DATE
Do not use later than the date of expiry.
STORAGE
Store below 25^oC. Do not freeze.
PRESENTATION
Tide Injection is available in 2 ml ampoules.

Marketed by :
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TORRENT PHARMACEUTICALS LTD.
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