1. NAME OF THE MEDICINAL PRODUCT

Torsemide Tablets

TORSINEX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains: Torsemide USP 10mg

Each uncoated tablet contains: Torsemide USP 20mg

Each uncoated tablet contains: Torsemide USP 100mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Torsinex 10: White flat, circular, bevel edged uncoated tablets with ML engraved on one surface and breakline on other surface

TORSINEX 20: White flat, circular, bevel edged uncoated tablets with ML engraved on one surface

TORSINEX 100: White flat, circular, bevel edged uncoated tablets with ML engraved on one surface

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Torsemide tablet 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. Torsemide tablets are indicated for the treatment of hypertension alone or in combination with other antihypertensive agents.

4.2 Posology and method of administration

General

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

Congestive Heart Failure

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

response is obtained. Single doses higher than 200 mg have not been adequately studied.

Chronic Renal Failure

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

Hepatic Cirrhosis

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

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

Hypertension

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

4.3 Contraindications

Torsemide tablet is contraindicated in patients with known hypersensitivity to torsemide or to sulfonylureas.

Torsemide tablet is contraindicated in patients who are anuric.

4.4 Special warnings and precautions for use

Hepatic Disease with Cirrhosis and Ascites

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

Ototoxicity

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

Volume and Electrolyte Depletion

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

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 0.1 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 hypomagnaesemia (1.3 mg/dL [0.53 mmol/L]) was reported as an adverse event.

In a long-term clinical study of torsemide 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 (0.7 mmol/L) was 6% and 9% in the groups receiving 5 mg and 10 mg of torsemide, respectively.

Blood Urea Nitrogen (BUN), Creatinine and Uric Acid

Torsemide produces small dose-related increases in each of these laboratory values. In hypertensive patients who received 10 mg of torsemide 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 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, 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 torsemide 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 torsemide 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 torsemide daily, no clinically significant differences from baseline lipid values were observed after 1 year of therapy.

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.

This medicine contains lactose, which is a type of sugar. If you have been told by your doctor that you cannot tolerate or digest some sugars (have intolerance to some sugars), talk to your doctor before taking this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Pregnancy and lactation

Pregnancy

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.

Lactation

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

4.7 Effects on ability to drive and use machines

As for other drugs which produce changes in blood pressure, patients taking Torasemide should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

4.8 Undesirable effects

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

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

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

	Torsemide Tablets	Placebo

	(N=564)	(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 torsemide used in these trials ranged from 1.25 mg to 20 mg, with most patients receiving 5 mg to 10 mg; the duration of treatment ranged from 1 to 52 days, with a median of 41 days. Of the side effects listed in the table, only "excessive urination" occurred significantly more frequently in patients treated with torsemide than in patients treated with placebo. In the placebo-controlled hypertension studies whose design allowed side-effect rates to be attributed to dose, excessive urination was reported by 1% of patients receiving placebo, 4% of those treated with 5 mg of daily torsemide, and 15% of those treated with 10 mg. The complaint of excessive urination was generally not reported as an adverse event among patients who received torsemide for cardiac, renal, or hepatic failure.

Serious adverse events reported in the clinical studies for which a drug relationship could not be excluded were atrial fibrillation, chest pain, diarrhea, digitalis intoxication, gastrointestinal hemorrhage, hyperglycemia, hyperuricaemia, hypokalemia, hypotension, hypovolemia, shunt thrombosis, rash, rectal bleeding, syncope, and ventricular tachycardia.
Angioedema has been reported in a patient exposed to torsemide who was later found to be allergic to sulfa drugs.

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

4.9 Overdose

There is no human experience with overdoses of torsemide, but the signs and symptoms of over dosage can be anticipated to be those of excessive pharmacologic effect: dehydration, hypovolemia, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, and haemoconcentration. Treatment of over dosage 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Micro puncture 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 +/2CI --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.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of torsemide tablets is approximately 80%, with little intersubject variation; the 90% confidence interval is 75% to 89%. The drug is absorbed with little first-pass metabolism, and the serum concentration reaches its peak (C max) within 1 hour after oral administration. C max and area under the serum concentration-time curve (AUC) after oral administration are proportional to dose over the range of 2.5 mg to 200 mg. Simultaneous food intake delays the time to C max by about 30 minutes, but overall bioavailability (AUC) and diuretic activity are unchanged. Absorption is essentially unaffected by renal or hepatic dysfunction.

Distribution

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.

Metabolism

Torasemide is metabolised to three metabolites, M1, M3 and M5 by stepwise oxidation, hydroxylation or ring hydroxylation.

Elimination

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.

5.3 Preclinical safety data

Chronic toxicity

The changes observed in toxicity studies in dogs and rats at high doses are attributable to an excess Pharmacodynamic action (diuresis). Changes observed were weight reduction, increases in creatinine and urea and renal alterations such as tubular dilatation and interstitial nephritis. All drug induced changes were shown to be reversible.

Carcinogenesis & Mutagenesis & 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.

6. Pharmaceutical Particulars

6.1 List of excipients

Lactose

Microcrystalline cellulose

Povidone

Crospovidone type-a

Colloidal anhydrous silica

Magnesium stearate

Talc

6.2 Incompatibilities

None known

6.3 Shelf life

36 Months from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C. Keep out from the reach of children.

6.5 Nature and contents of container

3x10, Alu/Alu Blister

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder:

MICRO LABS LIMITED

#31, Race Course Road

Bangalore-560001

INDIA

8. Marketing Authorization Numbers

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9. Date of first authorization

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10. Date of revision of text

July 2021