MELTOR™

Tablets

Composition:

Each Tablet contains

Torsemide 5/10/20/40/100mg

Pharmacokinetic properties:

Torsemide is well absorbed from the gastrointestinal tract. Peak serum concentrations are achieved within 1 hour of oral doses. Torsemide is metabolised by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. Metabolism takes place in the liver and inactive metabolites are excreted in the urine. The elimination half-life of Torsemide is about 3.5 hours. Torsemide is extensively bound to plasma proteins. In patients with heart failure both hepatic and renal clearance are reduced. In patients with renal impairment, the renal clearance is reduced but total plasma clearance is not significantly altered.

Mechanism of Action

Torasemide inhibits the $Na^+/K^+/2Cl^-$-carrier system (via interference of the chloride binding site) in the lumen of the thick ascending portion of the loop of Henle, resulting in a decrease in reabsorption of sodium and chloride. This results in an increase in the rate of delivery of tubular fluid and electrolytes to the distal sites of hydrogen and potassium ion secretion, while plasma volume contraction increases aldosterone production. The increased delivery and high aldosterone levels promote sodium reabsorption at the distal tubules, and By increasing the delivery of sodium to the distal renal tubule, torasemide indirectly increases potassium excretion via the sodium-potassium exchange mechanism. Torasemide's effects in other segments of the nephron have not been demonstrated. Thus torasemide 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.

Other pharmacodynamic properties:

Torasemide (INN) or torsemide (USAN) is a novel loop diuretic belonging to pyridine sulphonyl urea. It differs from other thiazide diuretics in that a double ring system is incorporated into its structure. Like thiazides, loop diuretics must be secreted into the tubular fluid by proximal tubule cells. In the thick ascending loop Na+ and Cl- reabsorption is accomplished by a $Na^+/K^+/2Cl^-$symporter. The thick ascending limb has a high reabsorptive

capacity and is responsible for reabsorbing 25% of the filtered load of Na^+. The loop diuretics act by blocking this symporter. Because of the large absorptive capacity and the amount of Na^+ delivered to the ascending limb, loop diuretics have a profound diuretic action. In addition, more distal nephron segments do not have the reabsorptive capacity to compensate for this increased load. The osmotic gradient for water reabsorption is also reduced resulting in an increase in the amount of water excreted. Torasemide's effects as a antihypertensive are due to its diuretic actions. By reducing extracellular and plasma fluid volume, blood pressure is reduced temporarily, and cardiac output also decreases.

Indication:

- Meltor is indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease and CKD.
- Meltor is indicated for the treatment of hypertension alone or in combination with other antihypertensive agents

Contraindication:

The use of Meltor is contraindicated in patients with:

- Known hypersensitivity to torsemide or to sulfonylureas
- Anuria (production of <50 mL urine/day)

Drug Interaction:

Nonsteroidal Anti-inflammatory Drugs

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.

Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and torsemide has been associated with the development of acute renal failure. The antihypertensive and diuretic effects of torsemide can be reduced by NSAIDs.

Partial inhibition of the natriuretic effect of torsemide by concomitant administration of indomethacin 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).

Cytochrome P450 2C9 Inhibitors and Inducers

Torsemide is a substrate of CYP2C9. Concomitant use of CYP2C9 inhibitors (e.g., amiodarone, fluconazole, miconazole, oxandrolone) can decrease torsemide clearance and increase torsemide plasma concentrations. Concomitant use of CYP2C9 inducers (e.g., rifampin) increase torsemide clearance and decrease plasma torsemide concentrations. Monitor diuretic effect and blood pressure when used in combination with CYP2C9 inhibitor or inducer. Adjust torsemide dose if necessary.

Because of its inhibition of CYP2C9 metabolism, torsemide may affect the efficacy and safety of sensitive CYP2C9 substrates, such as celecoxib, or of substrates with a narrow therapeutic range, such as warfarin or phenytoin. Monitor patients and adjust dosages if necessary.

Cholestyramine

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 should be coadministered, administer torsemide at least one hour before or 4 to 6 h after cholestyramine administration.

Organic Anion Drugs

Coadministration of organic anion drugs (e.g., probenecid) that undergo significant renal tubular secretion have the potential to reduce secretion of torsemide into the proximal tubule and thereby decreases the diuretic activity of torsemide. Monitor diuretic effect and blood pressure during coadministration.

Lithium

Like other diuretics, torsemide reduces the renal clearance of lithium, inducing a high risk of lithium toxicity. Monitor lithium levels periodically when torsemide is coadministered.

Ototoxic Drugs

Loop diuretics increase the ototoxic potential of other ototoxic drugs, including aminoglycoside antibiotics and ethacrynic acid. This effect has been reported with concomitant use of torsemide and gentamycin. Avoid concomitant use of torsemide and aminoglycoside antibiotics, if possible.

Renin-angiotensin Inhibitors

Coadministration of torsemide with ACE inhibitors or angiotensin receptor blockers can increase the risk of hypotension and renal impairment.

Radiocontrast Agents

Torsemide can increase the risk of renal toxicity related to administration of radiocontrast agents.

Corticosteroids and ACTH

Concomitant use with torsemide may increase risk of hypokalemia.

Adverse effects:

Dizziness, headache, nausea, weakness, vomiting, hyperglycemia, excessive urination, hyperuricemia, hypokalemia, excessive thirst, hypovolemia, impotence, esophageal hemorrhage, pancreatitis, leucopenia, thrombocytopenia and dyspepsia.

Overdosage

There is no human experience with overdoses of MELTOR, 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.

Warnings and Precautions:

- **Hepatic Disease**

With Cirrhosis and Ascites MELTOR 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 MELTOR (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 MELTOR.

- 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 MELTOR. It is not certain that these events were attributable to MELTOR. 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, bloodvolume 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, hyperor hypochloremia, hyper- or hypokalemia, acid-base abnormalities, and increased blood urea nitrogen (BUN). If any of these occur, MELTOR should be discontinued until the situation is corrected; MELTOR may be restarted at a lower dose. In controlled studies in the United States, MELTOR 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 MELTOR (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 MELTOR at doses higher than those studied in United

States antihypertensive trials, hypokalemia was observed with greater frequency, in a doserelated 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 MELTOR.

- **Laboratory Values**

Potassium: See WARNINGS.

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

Magnesium: Single doses of MELTOR 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 MELTOR 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 MELTOR 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 MELTOR, respectively.

Blood Urea Nitrogen (BUN), Creatinine and Uric Acid: MELTOR produces small dose-related increases in each of these laboratory values. In hypertensive patients who received 10 mg of MELTOR 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 MELTOR, but its incidence has been similar to that seen in patients receiving placebo.

Glucose: Hypertensive patients who received 10 mg of daily MELTOR 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 205 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 MELTOR 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 MELTOR 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 MELTOR daily, no clinically significant differences from baseline lipid values were observed after 1 year of therapy.

Other: In long-term studies in hypertensive patients, MELTOR 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.

Use in special population:

1. **Pediatric:** Safety and effectiveness in pediatric patients have not been established.
2. **Geriatric:** Appropriate studies performed to date have not demonstrated geriatric-specific problems that would limit the usefulness of torsemide in the elderly. However, elderly patients are more likely to have age-related liver, kidney, or heart problems, which may require caution and an adjustment in the dose for elderly patients
3. **Liver impairment:** Meltor should be used with caution in patients with hepatic disease
4. **Renal failure:** Use with caution.
5. **Pregnancy and lactation:** Pregnancy Category B. Meltor should be used during pregnancy only if clearly needed. Caution should be exercised when MELTOR is administered to a nursing woman

Dosage:

As directed by physician.

Presentation:

Meltor is available in a pack of 10 tablets.

Storage and handling:

Store below 30^{o}C in a dry place. Protect from light.