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

Tide

(Torsemide Tablets I.P. 5 mg, 10 mg, 20 mg and 100 mg)

COMPOSITION

Tide-5
Each uncoated tablet contains :
Torsemide I.P. 5 mg

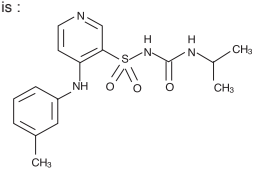
Tide-10
Each uncoated tablet contains :
Torsemide I.P. 10 mg

Tide-20
Each uncoated tablet contains :
Torsemide I.P. 20 mg

Tide-100
Each uncoated tablet contains :
Torsemide I.P. 100 mg

DESCRIPTION

Torsemide is a diuretic of the pyridine-sulfonylurea class. Its chemical name is 3-Pyridinesulfonamide, N-[[(1-methylethyl) amino]carbonyl]-4-[(3-methylphenyl) amino]-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 348.42.

Torsemide is a white to off-white, crystalline powder. Slightly soluble in 0.1 N sodium hydroxide, in 0.1 N hydrochloric acid, in alcohol, and in methanol; very slightly soluble in acetone and in chloroform; practically insoluble in water and in ether.

CLINICAL PHARMACOLOGY

Mechanism of Action

Torasemide is a loop diuretic. However, at low doses its pharmaco-dynamic profile resembles that of the thiazide class regarding the level and duration of diuresis. At higher doses, torasemide induces a brisk diuresis in a dose dependant manner with a high ceiling of effect. 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

Torsemide is well absorbed from the gastrointestinal tract. Peak serum concentrations are achieved within 1 hour of oral doses. Cmax 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 Cmax by about 30 minutes, but overall bioavailability (AUC) and diuretic activity are unchanged. Torsemide is metabolised by the cytochrome P450 isoenzyme CYP2C9, which shows genetic poly-morphism. 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 > 99 % bound to plasma proteins. The apparent distribution volume 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 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. 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

Tide is indicated for the treatment of oedema associated with congestive heart failure, renal or hepatic disease and essential hypertension.

CONTRAINDICATION

Torsemide is contraindicated in patients with known hypersensitivity to torsemide or to sulfonylureas. Torsemide is contraindicated in patients who are anuric.

Torsemide is contraindicated in hepatic coma and pre - coma; hypotension; pregnancy and lactation; cardiac arrhythmias, simultaneous therapy with aminoglycosides or cephalosporins, or renal dysfunction due to drugs which cause renal damage.

WARNINGS

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 reported after rapid intravenous injection of other loop diuretics and have also been reported after oral torsemide. It is not certain that these events were attributable to torsemide. Ototoxicity has also been reported 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 abnormal ities, 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 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. Careful monitoring of patients with a tendency to hyperuricaemia and gout is recommended. Carbohydrate metabolism in latent or manifest diabetes mellitus should be monitored.

PRECAUTIONS

Laboratory Values

Evidences reported that during torsemide treatment, electrolyte levels (calcium, magnesium), blood urea nitrogen, creatinine, uric acid, glucose, serum lipids levels were altered and should be monitored during therapy with torsemide. Clinical trials also reports that torsemide is associated with small mean decrease in hemoglobin, hematocrit, 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. 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. Patients with rare hereditary problems of glucose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medication.

Drug Interactions

During clinical trials the torsemide was given with beta-blockers, ACE inhibitors, calcium-channel blockers in hypertensive individuals, with digitalis glycoside, ACE inhibitors, organic nitrates in patients with congestive heart failure. 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 NSAIDs (including aspirin) have not been studied clinical trials, but 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 pharma-cokinetic profile and diuretic activity of torsemide are not altered by cimetidine or spironolactone. Coadmini-stration 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. The kaliuretic effect of mineralo-and glucocorticoids and laxatives may be increased. Torsemide potentiates the toxicity of cisplatin preparation, nephrotoxic effects of cephalosporins. The action of curare-containing muscle relaxants and of theophylline can be potentiated. Torasemide may decrease arterial responsiveness to pressor agents e.g. adrenaline, noradrenaline. Sequential or combined treatment or starting a new co-medication with an ACE inhibitor may result in transient hypotension. This may be minimised by lowering the starting dose of the ACE inhibitor and/or reducing or stopping temporarily the dose of torasemide. The action of anti-diabetic drugs may be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility

No overall increase in tumor incidence was reported 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 and Lactation

Pregnancy Category B.

There are no data from experience in humans of the effect of torsemide on the embryo and foetus. Whilst studies in the rat have shown no teratogenic effect, malformed foetuses have been observed after high doses in pregnant rabbits. No studies have been conducted on excretion in breast milk. Consequently,
torsemide is contra-indicated in pregnancy and lactation.

Labor and Delivery

The effect of torsemide on labor and delivery is unknown.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No specific age-related differences in effectiveness or safety were reported between younger patients and elderly patients.

ADVERSE REACTIONS

Blood chemistry/volume :

As with other diuretics, depending on the dosage and duration of treatment, there may be disturbances of water and electrolyte balance, especially with markedly limited salt intake. Hypokalaemia may occur (especially if a low potassium diet is being taken, or if vomiting, diarrhoea, or excessive use of laxatives takes place, or in cases of hepatic failure). Symptoms and signs of electrolyte and volume depletion, such as headache, dizziness, hypotension, weakness, drowsiness, confusional states, loss of appetite and cramps, can occur if diuresis is marked, especially at the start of treatment and in elderly patients. Dose adjustment may be necessary. Raised serum uric acid, glucose and lipids can occur. There may be aggravation of metabolic alkalosis.

Cardiovascular system :

In isolated cases, thromboembolic complications and circulatory disturbances due to haemoconcentration may occur. Other adverse events for which causal relationship can not be established were atrial fibrillation, ventricular tachycardia, shunt thrombosis, rectal bleeding, digitalis intoxication.

Gastro-intestinal system :

Patients may experience gastro-intestinal symptoms (vomiting, esophageal haemorrhage, dyspepsia, constipation etc.).

Pancreatitis

Renal and Urinary system:

In patients with urinary outflow obstruction, retention of urine may be precipitated. Raised serum urea and creatinine may occur, excessive urination,

Liver:

Increases in certain liver enzymes, eg. gamma-GT

Haematology:

Isolated cases of decreases in red and white blood cells and platelets have been reported.

Skin/allergy:

In isolated cases, there may be allergic reactions, such as pruritis, rash, angioedema, photosensitivity.

Nervous system:

Isolated reports of visual disturbance
Tinnitus and hearing loss have occurred in isolated cases. Rarely, limb paraesthesia has been reported.

Others:

Dry mouth, excessive thirst, hypovolaemia, impotence, rhinitis, asthenia, ECG abnormality, cough increased, arthralgia, sore throat, myalgia, chest pain, insomnia, nervousness, edema. **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 pharma-cologic 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.

DOSAGES AND ADMINISTRATION

Congestive Heart Failure

The usual initial dose is 10 mg or 20 mg of once-daily. 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. 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, 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 at a temperature not exceeding 30º C, in dry place

PRESENTATION

Tide 5/10/20/100 are available in strip of 10 tablets.

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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