For The use of registered medical practitioners only

Tide Plus

(Torsemide and Spironolactone Tablets)

COMPOSITION

Tide Plus 10

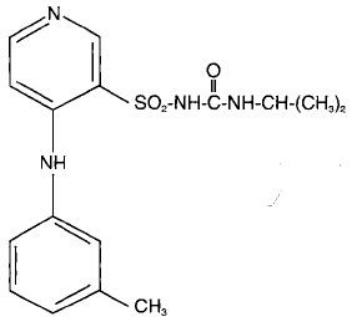
Each uncoated tablet contains:
Torsemide I.P. 10mg
Spironolactone I.P. 25mg

Tide Plus 20

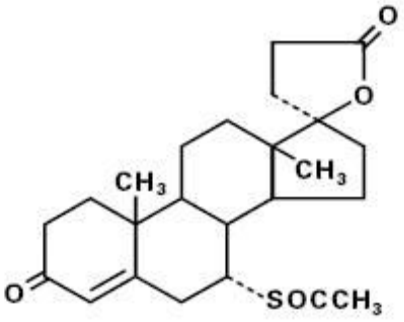
Each uncoated tablet contains:
Torsemide I.P 20mg
Spironolactone I.P. 25mg

DESCRIPTION

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



Spironolactone is aldosterone antagonist, is 17-hydroxy-7αmercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone acetate and has the following structural formula



CLINICAL PHARMACOLOGY

Torsemide

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 and Metabolism

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. 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 39 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.

Spironolactone

Mechanism of Action

Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. It may be given alone or with other diuretic agents which act more proximally in the renal tubule.

Aldosterone Antagonist Activity:

Increased levels of the mineralocorticoid, aldosterone, is present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and the nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for the edema and ascites in those conditions. Spironolactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by active diuretic therapy.

Spironolactone is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism. It is also effective in most cases of essential hypertension, despite the fact that aldosterone secretion may be within normal limits in benign essential hypertension. Through its action in antagonizing the effect of aldosterone, spironolactone inhibits the exchange of sodium for potassium in the distal renal tubule and helps to prevent potassium loss. Spironolactone has not been demonstrated to elevate serum uric acid, to precipitate gout, or to alter carbohydrate metabolism.

Pharmacokinetics:

Spironolactone is rapidly and extensively metabolized. Sulfur-containing products are the predominant metabolites and are thought to be primarily responsible, together with Spironolactone, for the therapeutic effects of the drug.

The following pharmacokinetic data were obtained from 12 healthy volunteers following the administration of 100 mg of spironolactone daily for 15 days. On the 15th day, spironolactone was given immediately after a low-fat breakfast and blood was drawn thereafter.

	Accumulation Factor: AUC $_{(0–24\ hr,\ day\ 15)}$/ AUC$_{(0–24\ hr,\ day\ 1)}$	**Mean Peak Serum Concentration**	**Mean (SD) Post Steady-State Half-Life**
7-α-(thiomethyl) spirolactone (TMS)	1.25	391 ng/mL at 3.2 hr	13.8 hr (6.4) (terminal)
6-β-hydroxy-7-α-	1.50	125 ng/mL at 5.1 hr	15.0 hr (4.0)

(thiomethyl) spirolactone (HTMS)			(terminal)
Canrenone (C)	1.41	181 ng/mL at 4.3 hr	16.5 hr (6.3) (terminal)
Spironolactone	1.30	80 ng/mL at 2.6 hr	Approximately 1.4 hr (0.5) (β half-life)

The pharmacological activity of spironolactone metabolites in man is not known. However, in the adrenalectomized rat the antimineralocorticoid activities of the metabolites C, TMS, and HTMS, relative to spironolactone were 1.10, 1.28, and 0.32, respectively. Relative to spironolactone, their binding affinities to the aldosterone receptors in rat kidney slices were 0.19, 0.86, and 0.06, respectively.

In humans, the potencies of TMS and 7-α-thiospirolactone in reversing the effects of the synthetic mineralocorticoid, fludrocortisone, on urinary electrolyte composition were 0.33 and 0.26, respectively, relative to spironolactone. However, since the serum concentrations of these steroids were not determined, their incomplete absorption and/or first-pass metabolism could not be ruled out as a reason for their reduced *in vivo* activities.

Spironolactone and its metabolites are more than 90% bound to plasma proteins. The metabolites are excreted primarily in the urine and secondarily in bile.

The effect of food on spironolactone absorption (two 100 mg Spironolactone tablets) was assessed in a single-dose study of 9 healthy, drug-free volunteers. Food increased the bioavailability of unmetabolized spironolactone by almost 100%. The clinical importance of this finding is not known.

INDICATIONS AND USAGE

For treatment of resistant oedema associated with chronic cardic failure, hepatic cirrhosis; resistant hypertension and secondary hyperaldosteronism.

DOSAGE AND ADMINISTRATION

One or two tablets once daily. Dose can be increased if there is no sufficient response. Maximum recommended dose of torasemide is 200mg/day and spironolcatone is 400mg/day

CONTRAINDICATIONS

Torsemide

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

Spironolactone
Spironolactone is contraindicated in patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, hypercalcemia, hyperkalemia, Addison's disease or other conditions associated with hyperkalemia, and with concomitant use of eplerenone.

WARNINGS AND PRECUTIONS

TORSEMIDE

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 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. 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 Torsemide 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 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.

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. 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 (0.70 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 changeoccurred 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 longterm 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.

SPIRONOLACTONE
Potassium supplementation:
Potassium supplementation, either in the form of medication or as a diet rich in potassium, should not ordinarily be given in association with spironolactone therapy. Excessive potassium intake may cause hyperkalemia in patients receiving spironolactone.

Concomitant administration of SPIRONOLACTONE with the following drugs or potassium sources may lead to severe hyperkalemia:

- Other potassium-sparing diuretics
- ACE inhibitors
- Angiotensin II receptor antagonists
- Aldosterone blockers
- Non-steroidal anti-inflammatory drugs (NSAIDs), e.g., indomethacin
- Heparin and low molecular weight heparin
- Other drugs or conditions known to cause hyperkalemia
- Potassium supplements
- Diet rich in potassium
- Salt substitutes containing potassium

Spironolactone should not be administered concurrently with other potassium-sparing diuretics. Spironolactone, when used with ACE inhibitors or indomethacin, even in the presence of a diuretic, has been associated with severe hyperkalemia. Extreme caution should be exercised when Spironolactone is given concomitantly with these drugs.

Hyperkalemia in patients with severe heart failure. Hyperkalemia may be fatal. It is critical to monitor and manage serum potassium in patients with severe heart failure receiving spironolactone. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium > 3.5 mEq/L. RALES excluded patients with a serum creatinine > 2.5 mg/dL or a recent increase in serum creatinine > 25%. The recommended monitoring for potassium and creatinine is one week after initiation or increase in dose of spironolactone, monthly for the first 3 months, then quarterly for a year, and then every 6 months. Discontinue or interrupt treatment for serum potassium > 5 mEq/L or for serum creatinine > 4 mg/dL.

Spironolactone should be used with caution in patients with impaired hepatic function because minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Lithium generally should not be given with diuretics.

Precautions

General: All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance, e.g., hypomagnesemia, hyponatremia, hypochloremic alkalosis, and hyperkalemia.

Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities, which may be fatal. Consequently, no potassium supplement should ordinarily be given with spironolactone.

If hyperkalemia is suspected (warning signs include paresthesia, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia, and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because mild hyperkalemia may not be associated with ECG changes.

If hyperkalemia is present, spironolactone should be discontinued immediately. With severe hyperkalemia, the clinical situation dictates the procedures to be employed. These may include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

Reversible hyperchloremic metabolic acidosis, usually in association with hyperkalemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.

Dilutional hyponatremia, manifested by dryness of the mouth, thirst, lethargy, and drowsiness, and confirmed by a low serum sodium level, may be caused or aggravated, especially when spironolactone is administered in combination with other diuretics, and dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of sodium, except in rare instances when the hyponatremia is life-threatening.

Spironolactone therapy may cause a transient elevation of BUN, especially in patients with pre-existing renal impairment. Spironolactone may cause mild acidosis.

Gynecomastia may develop in association with the use of spironolactone; physicians should be alert to its possible onset. The development of gynecomastia appears to be related to both dosage

level and duration of therapy and is normally reversible when spironolactone is discontinued. In rare instances, some breast enlargement may persist when spironolactone is discontinued.

Somnolence and dizziness have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

Information for patients:
Patients who receive Spironolactone should be advised to avoid potassium supplements and foods containing high levels of potassium including salt substitutes.

Laboratory tests:
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals, particularly in the elderly and those with significant renal or hepatic impairments.

DRUG INTERACTIONS
TORSEMIDE
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.

SPIRONOLACTONE:
ACE inhibitors Angiotensin II receptor antagonists, aldosterone blockers, potassium supplements, heparin, low molecular weight heparin, and other drugs known to cause hyperkalemia: Concomitant administration may lead to severe hyperkalemia.

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (e.g., oral agents, insulin): Dosage adjustment of the antidiabetic drug may be required (see Precautions).

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia, may occur.

Pressor amines (e.g., norepinephrine): Both spironolactone and hydrochlorothiazide reduce the vascular responsiveness to norepinephrine. Therefore, caution should be exercised in the management of patients subjected to regional or general anesthesia while they are being treated with Spironolactone.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant may result.

Lithium: Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Nonsteroidal anti-inflammatory drugs (NSAIDs): In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Combination of NSAIDs, e.g., indomethacin, with potassium-sparing diuretics has been associated with severe hyperkalemia. Therefore, when Spironolactone and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Digoxin: Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. Monitor serum digoxin levels and adjust dose accordingly. Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.

Cholestyramine: Hyperkalemic metabolic acidosis has been reported in patients given spironolactone concurrently with cholestyramine.

Drug/Laboratory test interactions: Thiazides should be discontinued before carrying out tests for parathyroid function (see Precautions: General). Thiazides may also decrease serum PBI levels without evidence of alteration of thyroid function.

Several reports of possible interference with digoxin radioimmunoassays by spironolactone or its metabolites have appeared in the literature. Neither the extent nor the potential clinical significance of its interference (which may be assay specific) has been fully established.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
TORSEMIDE
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.

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.

SPIRONOLACTONE:
Orally administered Spironolactone has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150, and 500 mg/ kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In a 24-month study in which the same strain of rat was administered doses of about 10, 30, 100, and 150 mg/kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal polyps in females.

A dose-related (above 20 mg/kg/day) incidence of myelocytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to Spironolactone and whose primary metabolite, canrenone, is also a major product of Torsemide for a period of one year. In two-year studies in the rat, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular, and mammary tumors.

Neither Spironolactone nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither Spironolactone nor potassium canrenoate has been shown to be mutagenic in mammalian tests *in vitro*. In the presence of metabolic activation, TIDE Spironolactone has been reported to be negative in some mammalian mutagenicity tests *in vitro* and inconclusive (but slightly positive) for mutagenicity in other mammalian tests *in vitro*. In the presence of metabolic activation, potassium canrenoate has been reported to test positive for mutagenicity in some mammalian tests *in vitro*, inconclusive in others, and negative in still others.

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg /kg/day, of Spironolactone there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups at 50 mg/kg/day. When injected into female rats (100 mg/kg/day for 7 days, i.p.), Spironolactone was found to increase the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a two-week post-treatment observation period. These effects were associated with retarded ovarian follicle development and a reduction in circulating estrogen levels, which would be expected to impair mating, fertility, and fecundity. Spironolactone (100 mg/kg/day), administered i.p. to female mice during a two-week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg, also increased the latency period to mating.

Pregnancy
Teratogenic effects
Pregnancy Category C
Teratology studies with Spironolactone have been carried out in mice and rabbits at doses of up to 20 mg/kg/day. On a body surface area basis, this dose in the mouse is substantially below the maximum recommended human dose and, in the rabbit, approximates the maximum recommended human dose. No teratogenic or other embryotoxic effects were observed in mice, but the 20 mg/kg dose caused an increased rate of resorption and a lower number of live fetuses in rabbits. Because of its antiandrogenic activity and the requirement of testosterone for male morphogenesis, Spironolactone may have the potential for adversely affecting sex differentiation of the male during embryogenesis. When administered to rats at 200 mg/kg/day between gestation days 13 and 21 (late embryogenesis and fetal development), feminization of male fetuses was observed.

Offspring exposed during late pregnancy to 50 and 100 mg/ kg/day doses of Spironolactone exhibited changes in the reproductive tract including dose-dependent decreases in weights of the ventral prostate and seminal vesicle in males, ovaries and uteri that were enlarged in females, and other indications of endocrine dysfunction, that persisted into adulthood. There are no adequate and well-controlled studies with Spironolactone in pregnant women.

Spironolactone has known endocrine effects in animals including progestational and antiandrogenic effects. The antiandrogenic effects can result in apparent estrogenic side effects in humans, such as gynecomastia. Therefore, the use of in pregnant mwomen requires that the anticipated benefit be weighed against the possible hazards to the fetus.

Nursing mothers
Canrenone, a major (and active) metabolite of, appears in human breast milk. Because has been found to be tumorigenic in rats, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. If use of the drug is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
TORSEMIDE
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.

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.

SPIRONOLACTONE
Digestive: Gastric bleeding, ulceration, gastritis, diarrhea and cramping, nausea, vomiting.

Reproductive: Gynecomastia (see Precautions), inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, breast pain. Carcinoma of the breast has been reported in patients taking spironolactone but a cause and effect relationship has not been established.

Hematologic: Leukopenia (including agranulocytosis), thrombocytopenia.

Hypersensitivity: Fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis.

Metabolism: Hyperkalemia, electrolyte disturbances (see Warnings and Precautions).

Musculoskeletal: Leg cramps.

Nervous system/psychiatric: Lethargy, mental confusion, ataxia, dizziness, headache, drowsiness.

Liver/biliary: A very few cases of mixed cholestatic/hepatocellular toxicity, with one reported fatality, have been reported with spironolactone administration.

Renal: Renal dysfunction (including renal failure).

Skin: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), alopecia, pruritus.

OVERDOSAGE

Torsemide

There is no human experience with overdoses of Spironolactone, 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 (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.

Spironolactone

The oral LD50 of Spironolactone is greater than 1000 mg/kg in mice, rats, and rabbits. Acute overdosage of Spironolactone may be manifested by drowsiness, mental confusion, maculopapular or erythematous rash, nausea, vomiting, dizziness, or diarrhea. Rarely, instances of hyponatremia, hyperkalemia, or hepatic coma may occur in patients with severe liver disease, but these are unlikely due to acute overdosage. Hyperkalemia may occur, especially in patients with impaired renal function.

Treatment

Induce vomiting or evacuate the stomach by lavage. There is no specific antidote. Treatment is supportive to maintain hydration, electrolyte balance, and vital functions. Patients who have renal impairment may develop spironolactone-induced hyperkalemia. In such cases, Spironolactone should be discontinued immediately. With severe hyperkalemia, the clinical situation dictates the procedures to be employed. These may include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

EXPIRY

Do not use later than the date of expiry

STORAGE

Store in a cool, dry & dark place. Keep out of reach of children.

PRESENTATION
Tide plus 10 and Tide plus 20 is available as Blister pack of 10 tablets

MARKETED BY


TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/TIDE PLUS/10,20,25mg/Apr-2015/03/PI