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

TIDE E

1. Generic Name

Combikit of Tablet A: Eplerenone Tablets I.P. and Tablet B: Torsemide Tablets I.P.

2. Qualitative and quantitative composition

TIDE E 10

Each combikit contains:

Tablet A:

Each film coated tablet contains:

Eplerenone I.P.…….25 mg

Excipients…….....q.s.

Colours: Yellow Oxide of Iron, Iron Oxide Red & Titanium Dioxide I.P.

Tablet B:

Each uncoated tablet contains:

Torsemide I.P.…….10 mg

Excipients…….....q.s.

TIDE E 20

Each combikit contains:

Tablet A:

Each film coated tablet contains:

Eplerenone I.P.…….25 mg

Excipients…….....q.s.

Colours: Yellow Oxide of Iron, Iron Oxide Red & Titanium Dioxide I.P.

Tablet B:

Each uncoated tablet contains:

Torsemide I.P.…….20 mg

Excipients…….....q.s.

The excipients used are Pregelatinised Starch, Lactose, Croscarmellose Sodium, Sodium Bicarbonate, Colloidal Silicon Dioxide, Talc, Sodium Stearyl Fumarate, Universal Film coat white, PEG 6000, Titanium Dioxide, Iron oxide Red, Yellow oxide of iron, Isopropyl alcohol, Microcrystalline Cellulose, Crospovidone, PVP-K30 and Magnesium Stearate.

3. Dosage form and strength

Dosage form: Film Coated tablet

Strength: 10 and 20 mg

4. Clinical particulars

4.1 Therapeutic indication

Congestive heart Failure Post-Myocardial infarction.

Eplerenone + Torsemide is indicated to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction <1=40%) and Clinical evidence of congestive heart failure after an acute myocardial Infarction.

Hypertension

Eplerenone + Torsemide is indicated for the treatment of hypertension to Lower blood pressure.

4.2 Posology and method of administration

Posology

In congestive heart Failure Post-Myocardial infarction.

The recommended starting dose of TIDE E is Eplerenone 25mg + Torsemide 10mg once daily. (The maximum daily dose of Eplerenone in CHF post Ml is50mg OD. The usual initial dose is 10 mg or20 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 with Torsemide). TIDE E may be administered with or without food.

Serum potassium should be measured before initiating Eplerenone + Torsemide therapy, within the first week and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter.

TIDE E has to be withheld when serum potassium >/=6.0 mEq/L. TIDE E can be restarted at when serum potassium levels have fallen below 5.5 mEq/L.

In hypertension

In patients with hypertension, the recommended dose of TIDE E is Eplerenone 25mg + Torsemide 10mg administered once daily. (The maximum daily dose of Eplerenone in Hypertension is 50mg BIO and that of Torsemide is 10mg OD).

Method of administration

Oral use

Tide E can be administered with or without a meal.

4.3 Contraindications

Eplerenone

Eplerenone is contraindicated in all patients with the following:

- Known or suspected hypersensitivity to Eplerenone
- Serum potassium >5.5 mEq/L at initiation
- Creatinine clearance <1=30 mUmin
- Concomitant use with the following potent CYP3A4 inhibitors: ketoconazole and ltraconazole.

Eplerenone is also contraindicated for the treatment of hypertension in patients with the following:

- Serum creatinine >2.0 mg/dl in males or> 1.8 mg/dl in females
- Creatinine clearance <50 mUmin
- Type 2 diabetes with microalbuminuria
- Concomitant use of potassium supplements or potassium-sparing
- Diuretics (amiloride, spironolactone, ortriamterene)

Torsemide

Contraindicated in patients with

- Known hypersensitivitytotorsemide or to sulfonylureas.
- In patients who are a uric.

4.4 Special warnings and precautions for use

Eplerenone

General:

Eplerenone should be administered cautiously in patients with:

- Concomitant administration of weak inhibitors of CYP3A4 (e.g., erythromycin, saquinavir, verapamil, fluconazole)
- Metabolic or respiratory acidosis (potentiation of hyperkalemic effects)

Hyperkalemia: Eplerenone can cause Hyperkalemia which can lead to serious, sometimes fatal, arrhythmias. This risk can be minimized by patient selection, avoidance of certain concomitant treatments, and monitoring. Periodic monitoring is recommended in patients at risk for the development of hyperkalemia (including patients receiving concomitant ACE inhibitors or angiotensin II receptor antagonists) until the effect of Eplerenone is established. Diabetic patients with CHF post-Ml, including those with proteinuria, should also be treated with caution (increased risk of hyperkalemia).

Patlanls wnh hepatic lnsufflolency: At steady state, Eplerenone Cmax and ALIC values increased by 3.6% and 42% in patients with moderate hepatic impairment (Child-Pugh Class B) versus healthy volunteers receiving Eplerenone 400mg once daily, and by 22% and 45% in patients aged > 65 years versus younger adults receiving Eplerenone 100mg once daily: however, these increases were not considered clinically significant. The use of Eplerenone in patients with severe hepatic impairment has not been evaluated.

Patlanls with renal Insufficiency: Patients with GHF post Ml who have serum creatinine levels >2.0 mg/dL (males) or >1.8 mg/dL (females) or creatinine clearance <1=50 ml/min should not be treated with Eplerenone (increased risk of hyperkalemia with declining renal function).

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 wereattributabletoTorsemide.

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 obseived 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 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.

Laboratory Values (Toreemide)

Potassium: See WARNINGS.

Calcium: Single doses of Torsemide increased the urinary excretion of calcium by normal subjects, but serum calcium levels were slightly increased in 4-to 6-week hypertension trials. In a long-term study of patients with congestive heart failure, the average 1-year change in serum calcium was a decrease of 0.1 O mg/dL (0.02 mmol/L).

Magnesium: Single doses of Torsemide caused healthy volunteers to increasetheirurinaryexcretion 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).

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 1 O mg of Torsemide daily for6 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-tenn 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, 1 O 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, 1 O 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-tenn studies of 5 mg to 20 mg of Torsemide daily, no clinically significant differences from baseline lipid values were observed after1 yearoftherapy.

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.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

Eplerenone

There was increased risk of carcinogenesis in heterozygous P53 deficient mice when tested for 6 months at dosages up to 1000 mg/kg/day (systemic AUG exposures up to 9 times the exposure in humans receiving the 100-mg/day therapeutic dose). Statistically significant increases in benign thyroid tumors were observed after 2 years in both male and female rats when administered Eplerenone 250 mg/kg/day (highest dose tested) and in male rats only at 75 mg/kg/day (systemic AUG exposures up to 2-12 times the exposure in humans receiving the 1 OD-mg/day therapeutic dose). Repeat dose administration of Eplerenone to rats increases the hepatic conjugation and clearance of thyroxin, which results in increased levels of TSH by a compensatory mechanism. Drugs that have produced thyroid tumors by this rodent-specific mechanism have not shown asimilar effect in humans.

Eplerenone was not shown to have any mutagenic potential. Decreased weights of seminal vesicies and epididymis and slightly decreased fertility was noticed in ma~ rats treated with Eplerenone at 1000 mg/kg/day for 10 weeks (AUG 17 times that at the 100- mg/day human therapeutic dose). Dose-related prostate atrophy was seen in dogs when Eplerenone was administered at dosages of 15 mg/kg/day and higher (AUG 5 times that at the 100-mg/day human therapeutic dose). Dogs with prostate atrophy did not show any decline in libido, sexual perfonnance, or semen quality.

Torsemide

No overall increase in tumor incidence was found when torsemidewas given to rats and micethroughouttheirlives. lnthe 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. Torsemide had no adverse effect on the reproductive performance of male or female rats.

4.5 Drugs interactions

Eplerenone

Inhibitors of GYP450 3A4: A 1.7-fold increase in Gmax of Eplerenone and a 5.4-fold increase in AUG of Eplerenone was seen when a single dose of Eplerenone 100 mg was administered with ketoconazole 200 mg BID, a potent inhibitor of the CYP3A4 pathway. Eplerenone should not be used with strong inhibitors of CYP450 3A4 (e.g., ketoconazole, itraconazole). Administration of Eplerenone with other CYP3A4 inhibitors (e.g.,

erythrornycin, verapamil, saquinavir and fluconazole) resulted in increases in Cmax of Eplerenone ranging from 1.4- to 1.6-fold and AUG from 2.0 to 2.9- fold.

ACE inhibitors and angiotensin II receptor blockers

The addition of Eplerenone 50-100 mg to angiotensin converting enzyme (ACE) inhibitors and angiontensin II receptor blockers (ARBs) increased mean serum potassium sligHy (about 0.09-0.13 meq/L). Because the concomitant use of another mineralocorticoid receptor blocker and ACE inhibitors or ARBs has led to clinically relevant hyperkalemia, caution should be used in administering Eplerenone with these drugs.

Lithium

Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Serum lithium levels should be monitored frequently if Eplerenone is administered concomitantly with llthium.

Nonsteroidal anti-inflammatoiy drugs (NSAIDs}

The administration of other potassium-sparing antihypertensives with NSAIDs has been shown to reduce the antihypertensive effect in some patients and result in severe hyperkalemia in patients with impaired renal function. Therefore, when Eplerenone and NSAIDs are used concomitantly, patients should be observed to determine whether the desired effect on blood pressure is obtained.

Torsemide

Protein binding

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 ALIC. However, clinical experience indicates that dosage adjustment of either agent is not required.

Salicylates and NSAIDs

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 antiinflammatory agents (including aspirin) have not been studied, coadministration of these agents with another loop diuretic (furosemide) has occasionally been associated with renal dysfunction.

Indomethacin

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).

Cimetidine spironolactone Digoxin

The pharmacokinetic profile and diuretic activity of torsemide are not altered by cimetidine orspironolactone. Coadministration of digoxin is reported to increase the area under the curve fortorsemide by 50%, but dose adjustment of Torsemide is not necessary. Cholestvramine: 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.

Probenecid

Coadministration of probenecid reduces secretion of Torsemide into the proximal tubule and thereby decreases the diuretic activityofTorsemide.

Lithium

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.

Aminoglycoside antibiotics and Ethacrynic acid

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 Use in special populations

Eplerenone

Pregnancy: Teratogenic effects

US FDA Pregnancy Category B There are no adequate and well controlled studies of Eplerenone in pregnant women. No teratogenic effects were seen in rats or rabbits, although decreased body weight in maternal rabbits and increased rabbit fetal resorptions and post-implantation loss were observed at the highest administered dosage. Eplerenone should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Torsemide

Pregnancy Category B. Adequate and well-controlled studies have not been carried out in pregnant women. Torsemide should be used during pregnancy only if clearly needed.

Nursing Mothers:

Eplerenone

Eplerenone and/or its metabolites are excreted into rat breast milk. It is not known whether Eplerenone is excreted into human breast milk; therefore, Eplerenone should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Torsemide

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:

Epleranone

The safety and efficacy of Eplerenone have not been established in pediatric patients.

Torsemide

Safety and effectiveness in pediatric patients have not been established.

Geriatric use

Eplerenone

No overall differences in safety or effectiveness have been observed between elder1y and younger hypertensive patients. No differences in overall incidence of adverse events were observed between elderly and younger patients with CHF post-Ml. However, due to age-related decreases in creatinine clearance, the incidence of laboratory-documented hyperkalemia was increased in patients 65 years and older.

Torsemide

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

4.7 Effects on ability to drive and use machines

No Data Availale

4.8 Undesirable effects

Eplerenone

Adverse events seen are mild and transient. Most commonly reported adverse events are headache, dizziness, fatigue, diarrhea, abdominal pain, coughing, influenza-like symptoms, albuminuria and lipid profile changes like hypercholesterolemia and hypertriglyceridemia. Gynecomastia and abnormal vaginal bleeding have occurred infrequently (less than 1%) in patients receiving Eplerenone. Elevated liver enzymes [Serum alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT)], reduction in serum sodium levels and increases in serum creatinine, blood urea nitrogen (BUN) and uric acid have been reported. Dose-related hyperkalemia has been reported during Eplerenone therapy. Angina pectoris and myocardial infarction have occurred in patients treated with Eplerenone.

Torsemide

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

Repored Postmarketing Experience: Adverse reactions reported include the following: leukopenia, thrombocytopenia. Serious skin reactions (i.e., Stevens-Johnson syndrome, toxic epidermal necrolysis) and Pancreatitis has been reported in association withtorsemide use.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Eplerenone

No cases of human overdosage with Eplerenone have been reported. The most likely manifestation of human overdosage would be anticipated to be hypotension or hyperkalemia. Eplerenone cannot be removed bY hemodialysis. Eplerenone has been shown to bind extensively to charcoal. If symptomatic hypotension should occur,

supportive treatment should be instiMed.11 hyperf<alemia develops, standard treatment should be initiated.

Torsemide

There is no human experience with overdoses of Torsemide, but the signs and symptoms of overdosage can be anticipated to be those of excessive pharmacologic effect: dehydration, hypovolemia, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, and hemoconcentration. Treabnent of overdosage should consist of fluid and electrolyte replacement. Torsemide is not dialyzable, so hemodialysis will not accelerate elimination.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Eplerenone

Eplerenone binds to the mineralocorticoid receptor and blocks the binding of aldosterone. Aldosterone synthesis, which occurs primarily in the adrenal gland, is modulated by angiotensin II, adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms.

Eplerenone, being an aldosterone antagonist, has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effect of Eplerenone on blood pressure.

Eplerenone has relative selectivity in binding to recombinant human mineralocorticoid receptors compared to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Torsemide

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. 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 glomerularfiltration rate, renal plasma flow, or acid-base balance.

5.2 Pharmacokinetic properties

Eplerenone

Absorption

Oral Eplerenone appears to be well absorbed. The absolute bioavailability of Eplerenone is unknown. Absorption is not affected by food. Maximum concentrations (Cmax) are achieved within 1 to 2 hrs (Tmax) after oral administration of Eplerenone.

Distribution

Eplerenone is 50% protein bound and is primarily bound to alpha-1-acid glycoprotein. Eplerenone does not preferentially bind to red blood cells. In healthy and hypertensive patients, the apparent volume of distribution at steady-state ranges from 43 to 90 L.

Metabolism

Eplerenone is extensively metabolized in the liver, primarily by cytochrome P4503A4. No active metabolites have been identified. Eplerenone is not an inhibitor of GYP1A2, CYP3A4, GYP2G19, GYP2G9, or CYP2D6. Eplerenone is not a substrate or inhibitor of P-Glycoprotein at clinically relevant doses.

Excretion

Less than 5% of a dose is excreted unchanged in the urine and feces. Following a single oral dose, approximately 67% of the dose was excreted in the urine and 32% of the dose was excreted in the feces. It is unknown if Eplerenone is excreted into human breast milk. Eplerenone and/or its metabolites are excreted into rat breast milk. The plasma elimination half- life is 3.5to 6 hours.

Torsemide

Absorption

The bioavailability of Torsemide is approximately 80%. The drug is absorbed with little first-pass metabolism, and the serum concentration reaches its peak (Cmax) within 1 hour after oral administration. Food delays the time to Cmax by about 30 minutes, but overall bioavailabilily (AUG) and diuretic activity are unchanged.

Distribution

The volume of distribution of torsemide is 12 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

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.

Excretion

The elimination half-life of torsemide is approximately 3.5 hours. 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 lnto tubular urine.

Special populations:

Age:

Eplerenone Torsemide: No specific age-related differences in effectiveness or safety were observed between younger patients and elderly patients.

Gender

Eplerenone

The pharmacokinetics of Eplerenone 100 mg once dally did not dlfferslgnlflcantly between males and females.

Renal insufficiency:

Eplerenone

Compared with healthy volunteers, steady-state Cmax and AUG values were increased by 24% and 38% in patients with severe renal impairment (creatinine clearance [CLCR] <1.8 LJh [<30 mUmin]) and decreased by 3% and 26% in patients undergoing haemodialysis.

Torsemide

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.

Hepatic Insufficiency:

Eplerenone

At steady state, Eplerenone Cmax and AUG values increased by 3.6% and 42% in patients with moderate hepatic impairment (Child-Pugh Class B) versus healthy volunteers receiving Eplerenone 400mg once daily, and by 22% and 45% in patients aged > 65 years versus younger adults receiving Eplerenone 100mg once daily; however, these increases were not considered clinically significant.

Torsemide

In patients with hepatic cirrhosis, the volume of distribution, plasma half-life, and renal clearance are all increased, but total clearance is unchanged.

De compensated heart failure

Torsamlde

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 ALIC 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.

6. Nonclinical properties

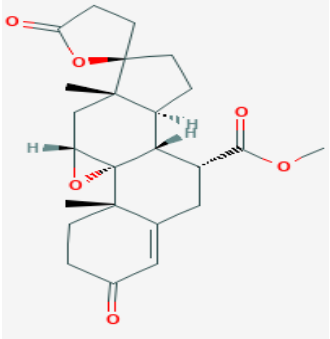
6.1 Animal Toxicology or Pharmacology

No data Available

7. Description

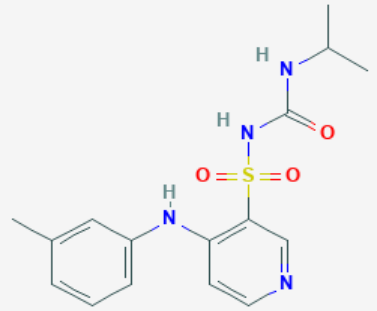
Eplerenone

Eplerenone is chemically, methyl (1*R*,2*S*,9*R*,10*R*,11*S*,14*R*,15*S*,17*R*)-2,15-dimethyl-5,5'-dioxospiro[18-oxapentacyclo[8.8.0.0^{1,17}.0^{2,7}.0^{11,15}]octadec-6-ene-14,2'-oxolane]-9-carboxylate having molecular formula of $C_{24}H_{30}O_6$ and molecular weight is 414.5g/mol. The chemical structure is:



Torsemide

Torsemide is chemically, 1-[4-(3-methylanilino)pyridin-3-yl]sulfonyl-3-propan-2-ylurea having molecular formula $C_{16}H_{20}N_4O_3S$ and molecular weight is 348.4g/mol. The chemical structure is:



Eplerenone Tablets are brown coloured, circular shaped, biconvex, film coated tablets, plain on both sides. The excipients used are Pregelatinised Starch, Lactose, Croscarmellose Sodium, Sodium Bicarbonate, Colloidal Silicon Dioxide, Talc, Sodium Stearyl Fumarate, Universal Film coat white, PEG 6000, Titanium Dioxide, Iron oxide Red, Yellow oxide of iron and Isopropyl alcohol.

Torsemide Tablets are white to off-white, caplet shaped, flat, bevel edged, uncoated tablets with break line on one side and plain on other side. The excipients used are Lactose, Microcrystalline Cellulose, Crospovidone, PVP K-30, Crospovidone and Magnesium Stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Tide E is 10 combikits of 10 Tablets of Eplerenone Tablets I.P. + 10 tablets of Torsemide Tablets I.P.

8.4 Storage and handing instructions

Store protected from moisture. At a temperature not exceeding 30°C.

9. Patient Counselling Information

Package leaflet: Information for the user

TIDE E

Tide E Film coated Tablets

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1 What TIDE E is and what it is used for

The active substance of **TIDE E** is Eplerenone and Torsemide.

What you need to know before you use TIDE E Do not take TIDE E:

- If you are allergic to Eplerenone and Torsemide or any of the other ingredients of this medicine. Do not take this medicine and talk to your doctor.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking TIDE E

Eplerenone

General:

Eplerenone should be administered cautiously in patients with:

- Concomitant administration of weak inhibitors of CYP3A4 (e.g., erythromycin, saquinavir, verapamil, fluconazole)
- Metabolic or respiratory acidosis (potentiation of hyperkalemic effects)

Hyperkalemia: Eplerenone can cause Hyperkalemia which can lead to serious, sometimes fatal, arrhythmias. This risk can be minimized by patient selection, avoidance of certain concomitant treatments, and monitoring. Periodic monitoring is recommended in patients at risk for the development of hyperkalemia (including patients receiving concomitant ACE inhibitors or angiotensin II receptor antagonists) until the effect of Eplerenone is established. Diabetic patients with CHF post-Ml, including those with proteinuria, should also be treated with caution (increased risk of hyperkalemia).

Patlanls wnh hepatic lnsufflolency: At steady state, Eplerenone Cmax and ALIC values increased by 3.6% and 42% in patients with moderate hepatic impairment (Child-Pugh Class B) versus healthy volunteers receiving Eplerenone 400mg once daily, and by 22% and 45% in patients aged > 65 years versus younger adults receiving Eplerenone 100mg once daily: however, these increases were not considered clinically significant. The use of Eplerenone in patients with severe hepatic impairment has not been evaluated.

Patlanls with renal Insufficiency: Patients with GHF post Ml who have serum creatinine levels >2.0 mg/dL (males) or >1.8 mg/dL (females) or creatinine clearance <1=50 ml/min should not be treated with Eplerenone (increased risk of hyperkalemia with declining renal function).

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 wereattributabletoTorsemide.

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 obseived 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 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.

Laboratory Values (Toreemide)

Potassium: See WARNINGS.

Calcium: Single doses of Torsemide increased the urinary excretion of calcium by normal subjects, but serum calcium levels were slightly increased in 4-to 6-week hypertension trials. In a long-term study of patients with congestive heart failure, the average 1-year change in serum calcium was a decrease of 0.1 O mg/dL (0.02 mmol/L).

Magnesium: Single doses of Torsemide caused healthy volunteers to increasetheirurinaryexcretion 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).

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 1 O mg of Torsemide daily for6 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-tenn 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, 1 O 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, 1 O 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-tenn studies of 5 mg to 20 mg of Torsemide daily, no clinically significant differences from baseline lipid values were observed after1 yearoftherapy.

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.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

Eplerenone

There was increased risk of carcinogenesis in heterozygous P53 deficient mice when tested for 6 months at dosages up to 1000 mg/kg/day (systemic AUG exposures up to 9 times the exposure in humans receiving the 100-mg/day therapeutic dose). Statistically significant increases in benign thyroid tumors were observed after 2 years in both male and female rats when administered Eplerenone 250 mg/kg/day (highest dose tested) and in

male rats only at 75 mg/kg/day (systemic AUG exposures up to 2-12 times the exposure in humans receiving the 1 OD-mg/day therapeutic dose). Repeat dose administration of Eplerenone to rats increases the hepatic conjugation and clearance of thyroxin, which results in increased levels of TSH by a compensatory mechanism. Drugs that have produced thyroid tumors by this rodent-specific mechanism have not shown asimilar effect in humans.

Eplerenone was not shown to have any mutagenic potential. Decreased weights of seminal vesicies and epididymis and slightly decreased fertility was noticed in ma~ rats treated with Eplerenone at 1000 mg/kg/day for 10 weeks (AUG 17 times that at the 100- mg/day human therapeutic dose). Dose-related prostate atrophy was seen in dogs when Eplerenone was administered at dosages of 15 mg/kg/day and higher (AUG 5 times that at the 100-mg/day human therapeutic dose). Dogs with prostate atrophy did not show any decline in libido, sexual perfonnance, or semen quality.

Torsemide

No overall increase in tumor incidence was found when torsemidewas given to rats and micethroughouttheirlives. lnthe 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. Torsemide had no adverse effect on the reproductive performance of male or female rats.

9.2 How to use TIDE E

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take and when

The amount of **TIDE E** people have to take varies depending on their condition. Your doctor will tell you exactly how many tablets of **TIDE E** to take.

How to take TIDE E

- Swallow the tablets whole with some water.

How long to take TIDE E

- Take TIDE E every day for as long as your doctor tells you. You may have to take this treatment over a long period of time.
- Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.
- If you take more TIDE E than you should
- If you take too many TIDE E tablets, or if someone else has taken your medicine, talk to your doctor straight away. Medical attention may be needed. If you need to see a doctor or go to the hospital, take the pack with you.

If you forget to take TIDE E

If you forget to take a dose of this medicine, take it as soon as you remember. Then take your next dose at the usual time. If it is almost time for your next dose, skip the dose you

missed. Do not take a double dose to make up for a forgotten tablet.

If you stop taking TIDE E

Do not stop taking TIDE E unless your doctor tells you to. If you have questions about how long to take this medicine, talk to your doctor.

9.3 Possible Side Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Eplerenone

Adverse events seen are mild and transient. Most commonly reported adverse events are headache, dizziness, fatigue, diarrhea, abdominal pain, coughing, influenza-like symptoms, albuminuria and lipid profile changes like hypercholesterolemia and hypertriglyceridemia. Gynecomastia and abnormal vaginal bleeding have occurred infrequently (less than 1%) in patients receiving Eplerenone. Elevated liver enzymes [Serum alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT)], reduction in serum sodium levels and increases in serum creatinine, blood urea nitrogen (BUN) and uric acid have been reported. Dose-related hyperkalemia has been reported during Eplerenone therapy. Angina pectoris and myocardial infarction have occurred in patients treated with Eplerenone.

Torsemide

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

Repored Postmarketing Experience: Adverse reactions reported include the following: leukopenia, thrombocytopenia. Serious skin reactions (i.e., Stevens-Johnson syndrome, toxic epidermal necrolysis) and Pancreatitis has been reported in association withtorsemide use.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.4 How to store TIDE E

Store protected from moisture. At a temperature not exceeding 30°C.

9.5 Contents of the pack and other information

What TIDE E contain:

Tide E is 10 combikits of 10 Tablets of Eplerenone Tablets I.P. + 10 tablets of Torsemide Tablets I.P.

Eplerenone Tablets are brown coloured, circular shaped, biconvex, film coated tablets, plain on both sides. The excipients used are Pregelatinised Starch, Lactose, Croscarmellose Sodium, Sodium Bicarbonate, Colloidal Silicon Dioxide, Talc, Sodium Stearyl Fumarate, Universal Film coat white, PEG 6000, Titanium Dioxide, Iron oxide Red, Yellow oxide of iron and Isopropyl alcohol.

Torsemide Tablets are white to off-white, caplet shaped, flat, bevel edged, uncoated tablets with break line on one side and plain on other side. The excipients used are Lactose, Microcrystalline Cellulose, Crospovidone, PVP K-30, Crospovidone and Magnesium Stearate.

Details of manufacturer

Torrent Pharmaceuticals Limited.

10 Details of permission or licence number with date

TIDE E

Mfg Lic No. M/750/2016 issued on 13.08.2021

11 Date of revision

JUNE 2022

MARKETED BY

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/TIDE E/ MAY-2022/01/PI