Tvaptan

Tablets

Composition:

Each tablet contains:

Tolvaptan 15/30mg

Pharmacokinetic properties:

In healthy subjects the pharmacokinetics of tolvaptan after single doses of up to 480 mg and multiple doses up to 300 mg once daily have been examined. Area under the curve (AUC) increases proportionally with dose. After administration of doses ≥60 mg, however, Cmax increases less than proportionally with dose. The pharmacokinetic properties of tolvaptan are stereospecific, with a steady-state ratio of the S-(-) to the R-(+) enantiomer of about 3. The absolute bioavailability of tolvaptan is unknown. At least 40% of the dose is absorbed as tolvaptan or metabolites. Peak concentrations of tolvaptan are observed between 2 and 4 hours post-dose. Food does not impact the bioavailability of tolvaptan. In vitro data indicate that tolvaptan is a substrate and inhibitor of P-gp. Tolvaptan is highly plasma protein bound (99%) and distributed into an apparent volume of distribution of about 3 L/kg. Tolvaptan is eliminated entirely by non-renal routes and mainly, if not exclusively, metabolized by CYP 3A. After oral dosing, clearance is about 4 mL/min/kg and the terminal phase half-life is about 12 hours. The accumulation factor of tolvaptan with the once daily regimen is 1.3 and the trough concentrations amount to ≤16% of the peak concentrations, suggesting a dominant half-life somewhat shorter than 12 hours. There is marked inter-subject variation in peak and average exposure to tolvaptan with a percent coefficient of variation ranging between 30 and 60%. In patients with hyponatremia of any origin the clearance of tolvaptan is reduced to about 2 mL/min/kg. Moderate or severe hepatic impairment or congestive heart failure decrease the clearance and increase the volume of distribution of tolvaptan, but the respective changes are not clinically relevant. Exposure and response to tolvaptan in subjects with creatinine clearance ranging between 79 and 10 mL/min and patients with normal renal function are not different. In a study in patients with creatinine clearances ranging from 10-124 mL/min administered a single dose of 60 mg tolvaptan, AUC and Cmax of plasma tolvaptan were less than doubled in patients with severe renal impairment relative to the controls. The peak increase in serum sodium was 5-6 mEq/L, regardless of renal function, but the onset and offset of tolvaptan's effect on serum sodium were slower in patients with severe renal impairment.

Mechanism of Action:

Tolvaptan is a selective and competitive arginine vasopressin receptor 2 antagonist. Vasopressin acts on the V2 receptors found in the walls of the vasculature and luminal membranes of renal collecting ducts. By blocking V2 receptors in the renal collecting ducts, aquaporins do not insert themselves into the walls thus preventing water absorption. This action ultimately results in an increase in urine volume, decrease urine osmolality, and increase electrolyte-free water clearance to reduce intravascular volume and an increase serum sodium levels. Tolvaptan is especially useful for heart failure patients as they have higher serum levels of vasopressin.

Other pharmacodynamic properties:

Urine volume and fluid intake increase in a dose dependent manner which results in overall negative fluid balance in patients taking tolvaptan. Increases in serum sodium and osmolality can be observed 4-8 hours post-administration and is maintained for 24 hours. The magnitude of serum sodium and osmolality change increases with escalating doses. Furthermore, a decrease in urine osmolality and increase in free water clearance can be observed 4 hours after post-administration of tolvaptan. The affinity for V2 receptors is 29x greater than that of V1a receptors and does not have any appreciable affinity for V2 receptors.

Indication:

Tolvaptan is indicated for the treatment of clinically significant hypervolemia and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with:

- Congestive Heart Failure (CHF)
- Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Contraindication:

Tolvaptan is contraindicated in the following conditions:

- Urgent need to raise serum sodium acutely

Tolvaptan has not been studied in a setting of urgent need to raise serum sodium acutely.

Inability of the patient to sense or appropriately respond to thirst Patients who are unable to auto-regulate fluid balance are at substantially increased risk of incurring an overly rapid correction of serum sodium, hypernatremia and hypovolemia.

- Hypovolemic hyponatremia

Risks associated with worsening hypovolemia, including complications such as hypotension and renal failure, outweigh possible benefits.

- Concomitant use of strong CYP 3A inhibitors

Ketoconazole 200 mg administered with tolvaptan increased tolvaptan exposure by 5-fold. Larger doses would be expected to produce larger increases in tolvaptan exposure. There is not adequate experience to define the dose adjustment that would be needed to allow safe use of Tolvaptan with strong CYP 3A inhibitors such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin.

- Anuric patients

In patients unable to make urine, no clinical benefit can be expected.

Drug Interaction:

- CYP 3A Inhibitors

Tolvaptan is a substrate of CYP 3A. CYP 3A inhibitors can lead to a marked increase in tolvaptan concentrations. Do not use tolvaptan with strong inhibitors of CYP 3A and avoid concomitant use with moderate CYP 3A inhibitors.

- CYP 3A Inducers

Avoid co-administration of CYP 3A inducers (e.g., rifampin, rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine, St. John's Wort) with tolvaptan, as this can lead to a reduction in the plasma concentration of tolvaptan and decreased effectiveness of tolvaptan treatment. If coadministered with CYP 3A inducers, the dose of tolvaptan may need to be increased.

- P-gp Inhibitors

The dose of tolvaptan may have to be reduced when tolvaptan is co-administered with P-gp inhibitors, e.g., cyclosporine.

- Hyperkalemia or Drugs that Increase Serum Potassium

Treatment with tolvaptan is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium. Serum potassium levels should be monitored after initiation of tolvaptan treatment in patients with a serum potassium >5 mEq/L as well as those who are receiving drugs known to increase serum potassium levels.

Adverse effects:

Blood and Lymphatic System Disorders: Disseminated intravascular coagulation

Cardiac Disorders: Intracardiac thrombus, ventricular fibrillation

Investigations: Prothrombin time prolonged

Gastrointestinal Disorders: Ischemic colitis

Metabolism and Nutrition Disorders: Diabetic ketoacidosis

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis

Nervous System: Cerebrovascular accident

Renal and Urinary Disorders: Urethral hemorrhage

Reproductive System and Breast Disorders (female): Vaginal hemorrhage

Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary embolism, respiratory failure

Vascular disorder: Deep vein thrombosis.

Warnings and Precautions:

- Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae

Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. In controlled clinical trials in which tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan-treated subjects with a serum sodium <130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium <130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours. None of the patients in these studies had evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too-rapid correction of serum sodium. Patients treated with tolvaptan should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving tolvaptan who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with tolvaptan and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with tolvaptan may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

- Gastrointestinal Bleeding in Patients with Cirrhosis

In patients with cirrhosis treated with olvaptan in hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo-treated patients. tolvaptan should be used in cirrhotic patients only when the need to treat outweighs this risk.

- Dehydration and Hypovolemia

Tolvaptan therapy induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especiallyin potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with tolvaptan, the incidence of dehydration was 3.3% for tolvaptan and 1.5% for placebo-treated patients. In patients receiving tolvaptan who develop medically significant signs or symptoms of hypovolemia, interrupt or discontinue tolvaptan therapy and provide supportive care with careful management of vital signs, fluid balance and electrolytes. Fluid restriction during therapy with tolvaptan may increase the risk of dehydration and hypovolemia. Patients receiving tolvaptan should continue ingestion of fluid in response to thirst.

- Co-administration with Hypertonic Saline

There is no experience with concomitant use of tolvaptan and hypertonic saline. Concomitant use with hypertonic saline is not recommended.

WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM

Tolvaptan should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g.,>12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seziures, coma and death. In suspectible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable

Use in special population:

1. **Pediatric:** Safety and effectiveness of tolvaptan in pediatric patients have not been established.
2. **Geriatric:** Of the total number of hyponatremic subjects treated with tolvaptan in clinical studies, 42% were 65 and over, while 19% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Increasing age has no effect on tolvaptan plasma concentrations.
3. **Liver impairment:** Moderate and severe hepatic impairment do not affect exposure to tolvaptan to a clinically relevant extent. No dose adjustment of tolvaptan is necessary.
4. **Renal failure**: No dose adjustment is necessary based on renal function. There are no clinical trial data in patients with CrCl <10 mL/min, and, because drug effects on serum sodium levels are likely lost at very low levels of renal function, use in patients

with a CrCl <10 mL/min is not recommended. No benefit can be expected in patients who are anuric.

5. **Pregnancy and lactation:** Pregnancy Category C. There are no adequate and well controlled studies of tolvaptan use in pregnant women. Tolvaptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether tolvaptan is excreted into human milk. Tolvaptan is excreted into the milk of lactating rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from tolvaptan, a decision should be made to discontinue nursing or tolvaptan, taking into consideration the importance of tolvaptan to the mother.

Dosage:

As directed by physician.

Presentation:

Tvaptan tablets are available in 15 mg and 30 mg tablets in blister pack of 4 Tablets

Storage and handling:

Store below 30^{o}C. Protect from light and moisture