Tvaptan®

Tvaptan® Tablets 15 mg

Label claim:

Each uncoated tablet contains:

Tolvaptan ..... 15 mg

Colour: Brilliant blue FCF

Tvaptan® Tablets 30 mg

Label claim:

Each uncoated tablet contains:

Tolvaptan ..... 30 mg

Colour: Brilliant blue FCF

Chemical Name: (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide.

Empirical formula: C H ClN O 26 25 2 3

Molecular weight: 448.94

CLINICAL PHARMACOLOGY

Mechanism of Action

Tolvaptan is a selective vasopressin V2-receptor antagonist with an affinity for the V2-receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan affinity for the V2-receptor is 29 times greater than for the V1a-receptor. When taken orally, 15 to 60 mg doses of Tolvaptan antagonize the effect of vasopressin and cause an increase in urine water excretion that results in an increase in free water clearance (aquaresis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations. Urinary excretion of sodium and potassium and plasma potassium concentrations are not significantly changed. Tolvaptan metabolites have no or weak antagonist activity for human V2-receptors compared with tolvaptan.

Plasma concentrations of native AVP may increase (avg. 2-9 pg/mL) with tolvaptan administration.

Pharmacodynamics

In healthy subjects receiving a single dose of tolvaptan 60 mg, the onset of the aquaretic and sodium increasing effects occurs within 2 to 4 hours post-dose. A peak effect of about a 6 mEq increase in serum sodium and about 9 mL/min increase in urine excretion rate is observed between 4 and 8 hours post-dose; thus, the pharmacological activity lags behind the plasma concentrations of tolvaptan. About 60% of the peak effect on serum sodium is sustained at 24 hours post-dose, but the urinary excretion rate is no longer elevated by this time. Doses above 60 mg tolvaptan do not increase aquaresis or serum sodium further. The effects of tolvaptan in the recommended dose range of 15 to 60 mg once daily appear to be limited to aquaresis and the resulting increase in sodium concentration.

In a parallel-arm, double-blind (for tolvaptan and placebo), placebo- and positive-controlled, multiple dose study of the effect of tolvaptan on the QTc interval, 172 healthy subjects were randomized to tolvaptan 30 mg, tolvaptan 300 mg, placebo, or moxifloxacin 400 mg once daily. At both the 30 mg and 300 mg doses, no significant effect of administering tolvaptan on the QTc interval was detected on Day 1 and Day 5. At the 300 mg dose, peak tolvaptan plasma concentrations were approximately 4-fold higher than the peak concentrations following a 30 mg dose. Moxifloxacin increased the QT interval by 12 ms at 2 hours after dosing on Day 1 and 17 ms at 1 hour after dosing on Day 5, indicating that the study was adequately designed and conducted to detect tolvaptan's effect on the QT interval, had an effect been present.

Pharmacokinetics

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 $\geq$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.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Up to two years of oral administration of tolvaptan to male and female rats at doses up to 1000 mg/kg/day (162 times the maximum recommended human dose [MRHD] on a body surface area basis), to male mice at doses up to 60 mg/kg/day (5 times the MRHD) and to female mice at doses up to 100 mg/kg/day (8 times the MRHD) did not increase the incidence of tumors.

Tolvaptan tested negative for genotoxicity in *in vitro* (bacterial reverse mutation assay and chromosomal aberration test in Chinese hamster lung fibroblast cells) and *in vivo* (rat micronucleus assay) test systems.

In a fertility study in which male and female rats were orally administered tolvaptan at 100, 300 or 1000 mg/kg/day, the highest dose level was associated with significantly fewer corpora lutea and implants than control.

Reproductive and Developmental Toxicology

In pregnant rats, oral administration of tolvaptan at 10, 100 and 1000 mg/kg/day during organogenesis was associated with a reduction in maternal body weight gain and food consumption at 100 and 1000 mg/kg/day, and reduced fetal weight and delayed ossification of fetuses at 1000 mg/kg/day (162 times the MRHD on a body surface area basis). Oral administration of tolvaptan at 100, 300 and 1000 mg/kg/day to pregnant rabbits during organogenesis was associated with reductions in maternal body weight gain and food consumption at all doses, and abortions at mid- and high-doses.

At 1000 mg/kg/day (324 times the MRHD), increased incidences of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations were observed. There are no adequate and well-controlled studies of tolvaptan in pregnant women.

tolvaptan should be used in pregnancy only if the potential benefit justifies the risk to the fetus.

INDICATIONS AND USAGE

Tolvaptan is indicated for the treatment of clinically significant hypervolemic 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 :

Hypervolemic Hyponatremia

- Congestive Heart Failure (CHF)

Euvolemic Hyponatremia

- Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Important Limitations

Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with tolvaptan.

It has not been established that raising serum sodium with tolvaptan provides a symptomatic benefit to patients.

DOSAGE AND ADMINISTRATION

Usual Dosage in Adults

Patients should be in a hospital for initiation and re-initiation of therapy to evaluate the therapeutic response and because too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death.

The usual starting dose for tolvaptan is 15 mg administered once daily without regard to meals. Increase the dose to 30 mg once daily, after at least 24 hours, to a maximum of 60 mg once daily, as needed to achieve the desired level of serum sodium. During initiation and titration, frequently monitor for changes in serum electrolytes and volume. Avoid fluid restriction during the first 24 hours of therapy. Patients receiving tolvaptan should be advised that they can continue ingestion of fluid in response to thirst.

Drug Withdrawal

Following discontinuation from tolvaptan, patients should be advised to resume fluid restriction and should be monitored for changes in serum sodium and volume status.

Co-Administration with CYP 3A Inhibitors, CYP 3A Inducers and P-gp Inhibitors

CYP 3A Inhibitors

Tolvaptan is metabolized by CYP 3A, and use with strong CYP 3A inhibitors causes a marked (5-fold) increase in exposure. The effect of moderate CYP 3A inhibitors on tolvaptan exposure has not been assessed. Avoid co-administration of tolvaptan and moderate CYP 3A inhibitors.

CYP 3A Inducers

Co-administration of tolvaptan with potent CYP 3A inducers (e.g., rifampin) reduces tolvaptan plasma concentrations by 85%. Therefore, the expected clinical effects of tolvaptan may not be observed at the recommended dose. Patient response should be monitored and the dose adjusted accordingly.

P-gp Inhibitors

Tolvaptan is a substrate of P-gp. Co-administration of tolvaptan with inhibitors of P-gp (e.g., cyclosporine) may necessitate a decrease in Tolvaptan dose.

DOSAGE FORMS AND STRENGTHS

Tolvaptan tablets are available in 15 mg and 30 mg tablets.

CONTRAINDICATIONS

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.

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 tolvaptan 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, mustim, 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.

Drug Interactions

Other Drugs Affecting Exposure to Tolvaptan

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 REACTIONS

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.

DRUG INTERACTIONS

Effects of Drugs on Tolvaptan

Ketoconazole and Other Strong CYP 3A Inhibitors

Tolvaptan is metabolized primarily by CYP 3A. Ketoconazole is a strong inhibitor of CYP 3A and also an inhibitor of P-gp. Co-administration of tolvaptan and ketoconazole 200 mg daily results in a 5-fold increase in exposure to tolvaptan. Co-administration of tolvaptan with 400 mg ketoconazole daily or with other strong CYP 3A inhibitors (e.g., clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, ritonavir and nefazodone) at the highest labeled dose would be expected to cause an even greater increase in tolvaptan exposure. Thus, tolvaptan and strong CYP 3A inhibitors should not be co-administered.

Moderate CYP 3A Inhibitors

The impact of moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem and verapamil) on the exposure to coadministered tolvaptan has not been assessed. A substantial increase in the exposure to tolvaptan would be expected when tolvaptan is coadministered with moderate CYP 3A inhibitors. Co-administration of tolvaptan with moderate CYP3A inhibitors should therefore generally be avoided.

Grapefruit Juice

Co-administration of grapefruit juice and tolvaptan results in a 1.8-fold increase in exposure to tolvaptan.

P-gp Inhibitors

Reduction in the dose of tolvaptan may be required in patients concomitantly treated with P-gp inhibitors, such as e.g., cyclosporine, based on clinical response.

Rifampin and Other CYP 3A Inducers

Rifampin is an inducer of CYP 3A and P-gp. Co-administration of rifampin and tolvaptan reduces exposure to tolvaptan by 85%. Therefore, the expected clinical effects of tolvaptan in the presence of rifampin and other inducers (e.g., rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine and St. John's Wort) may not be observed at the usual dose levels of tolvaptan. The dose of tolvaptan may have to be increased.

Lovastatin, Digoxin, Furosemide, and Hydrochlorothiazide

Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with tolvaptan has no clinically relevant impact on the exposure to tolvaptan.

Effects of Tolvaptan on Other Drugs

Digoxin

Digoxin is a P-gp substrate and tolvaptan is a P-gp inhibitor. Co-administration of tolvaptan and digoxin results in a 1.3-fold increase in the exposure to digoxin.

Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide

Co-administration of tolvaptan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or itsactive metabolite, desethylamiodarone) to a clinically significant degree.

Lovastatin

tolvaptan is a weak inhibitor of CYP 3A. Co-administration of lovastatin and tolvaptan increases the exposure to lovastatin and its active metabolite lovastatin-β hydroxyacid by factors of 1.4 and 1.3, respectively. This is not a clinically relevant change.

Pharmacodynamic Interactions

Tolvaptan produces a greater 24 hour urine volume/excretion rate than does furosemide or hydrochlorothiazide. Concomitant administration of tolvaptan with furosemide or hydrochlorothiazide results in a 24 hour urine volume/excretion rate that is similar to the rate after tolvaptan administration alone.

Although specific interaction studies were not performed, in clinical studies tolvaptan was used concomitantly with beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics. Adverse reactions of hyperkalemia were approximately 1-2% higher when tolvaptan was administered with angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics compared to administration of these medications with placebo. Serum potassium levels should be monitored during concomitant drug therapy.

USE IN SPECIFIC POPULATIONS

There is no need to adjust dose based on age, gender, race, or cardiac function.

Pregnancy

Pregnancy Category C.

There are no adequate and well controlled studies of tolvaptan use in pregnant women. In animal studies, cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased

fetal weight, delayed fetal ossification, and embryo-fetal death occurred. tolvaptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. Rats received 2 to 162 times the maximum recommended human dose (MRHD) of tolvaptan (on a body surface area basis). Reduced fetal weights and delayed fetal ossification occurred at 162 times the MRHD. Signs of maternal toxicity (reduction in body weight gain and food consumption) occurred at 16 and 162 times the MRHD. When pregnant rabbits received oral tolvaptan at 32 to 324 times the MRHD (on a body surface area basis), there were reductions in maternal body weight gain and food consumption at all doses, and increased abortions at the mid and high doses (about 97 and 324 times the MRHD). At 324 times the MRHD, there were increased rates of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations.

Labor and Delivery

The effect of tolvaptan on labor and delivery in humans is unknown.

Nursing Mothers

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.

Pediatric Use

Safety and effectiveness of tolvaptan in pediatric patients have not been established.

Geriatric Use

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.

Use in Patients with Hepatic Impairment

Moderate and severe hepatic impairment do not affect exposure to tolvaptan to a clinically relevant extent. No dose adjustment of tolvaptan is necessary.

Use in Patients with Renal Impairment

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.

Use in Patients with Congestive Heart Failure

The exposure to tolvaptan in patients with congestive heart failure is not clinically relevantly increased. No dose adjustment is necessary.

OVERDOSAGE

Single oral doses up to 480 mg and multiple doses up to 300 mg once daily for 5 days have been well tolerated in studies in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia.

The oral LD50 of tolvaptan in rats and dogs is >2000 mg/kg. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement should be considered.

Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated, which, if not matched by oral fluid ingestion, should be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.

ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (>99%). Close medical supervision and monitoring should continue until the patient recovers.

STORAGE

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

PACKING INFORMATION: Blister pack of 4 Tablets