

Samka^{Tablets}

(Tolvaptan)

سمکا
گولیاں
(ٹول وپٹن)

Composition:

Samka 15mg Tablets
Each un-coated tablet contains:
Tolvaptan15mg
(Innovator's Specs.)

Samka 30mg Tablets
Each un-coated tablet contains:
Tolvaptan30mg
(Innovator's Specs.)

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

See full prescribing information for complete boxed warning.

- **Samka** 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, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

Description:

Tolvaptan is a racemate comprising of equimolar amounts of @- and (S)-tolvaptan.Its Molecular Formula is C₂₈H₂₅ClN₂ O₃ and Molecular Weight 448.9 g/mol.

Therapeutic indications

Tolvaptan is used to treat hyponatremia (low sodium in the blood) in patients with heart failure or syndrome of inappropriate antidiuretic hormone (SIADH).

Tolvaptan is also used to slow kidney function decline in adults who are at risk of progressing autosomal dominant polycystic kidney disease (ADPKD).

Posology and method of administration

Posology:

Tolvaptan has to be initiated at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium.

Special populations:

Renal impairment: No dose adjustment is required in those with mild to moderate renal impairment.

Hepatic impairment: No information is available in patients with severe hepatic impairment.

Elderly: No dose adjustment is needed in elderly patients.

Dosage For ADPKD

Start (immediately upon waking up)at 45mg in AM and 15mg in PM , total daily dose is 60mg/day, Uptitrate by 15mg increments every 1-2 weeks to 60/30 or 90/30 if tolerated or until Uosm drops to less than 280 mOsm/L (before morning dose)

Note: Adjustment of tolvaptan dosage based on 24 hours urine osmolality measurements in patients with ADPKD .

Contraindications

Hypersensitivity to the active substance or to any of the excipients or to benzazepine or benzazepine derivatives, Anuria,Volume depletion, Hypovolemic hyponatremia, Hypematremia, Patients who cannot perceive thirst, Pregnancy, Breast-feeding.

Special warnings and precautions for use

Urgent need to raise serum sodium acutely: Tolvaptan has not been studied in a setting of urgent need to raise serum sodium acutely. For such patients, alternative treatment has to be considered.

Access to water: May cause adverse reactions related to water loss such as thirst, and dehydration

Dehydration: Volume status must be monitored in patients taking tolvaptan because severe dehydration can occur.

Urinary outflow obstruction: Patients with partial obstruction of urinary outflow, have an increased risk of developing acute retention.

Fluid and electrolyte balance: Fluid and electrolyte status has to be monitored in all patients and particularly in those with renal and hepatic impairment.

Too rapid correction of serum sodium: Patients with very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium

Diabetes mellitus: Tolvaptan may cause hyperglycemia.

Idiosyncratic hepatic toxicity: Liver injury induced by tolvaptan was observed in clinical trials.

Anaphylaxis: Patients have to be carefully monitored during treatment. Patients with known hypersensitivity reactions to benzazepine or benzazepine derivatives.

Interaction with other medicinal products and other forms of interaction

Co-administration with other treatments for hyponatremia and medicinal products that increase serum sodium concentration: Not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations where rapid correction may represent a risk for osmotic demyelination

Effect of other medicinal products on the pharmacokinetics of tolvaptan:

CYP3A4 inhibitors: Tolvaptan plasma concentrations have been increased by up to 5.4-fold area under time-concentration curve (AUC) after the administration of strong CYP3A4 inhibitors.

CYP3A4 inducers: Tolvaptan plasma concentrations have been decreased by up to 87 % (AUC) after the administration of CYP3A4 inducers. Caution has to be exercised

Effect of tolvaptan on the pharmacokinetics of other products:

CYP3A4 substrates: In healthy subjects, tolvaptan, a CYP3A4 substrate, had no effect on the plasma concentrations of some other CYP3A4 substrates (e.g., warfarin or amiodarone).

Transporter substrates:

P-glycoprotein substrates: Tolvaptan is a substrate and competitive inhibitor of P-glycoprotein. Patients receiving digoxin or other narrow therapeutic index P-gp substrates managed cautiously.

BCRP and OCT1: Co-administration of tolvaptan (90 mg) with rosuvastatin (5 mg), a BCRP substrate, increased rosuvastatin C_{max} and AUC_t of 54 % and 69 %, respectively.

Diuretics: Concomitant use of tolvaptan with loop and thiazide diuretics, each class of agent has the potential to lead to severe dehydration, which constitutes a risk factor for renal dysfunction.

Co-administration with vasopressin analogues: Tolvaptan is capable of blocking vascular vasopressin V2 receptors involved in the release of coagulation factors from endothelial cells.

Fertility, pregnancy and lactation

Pregnancy: The potential risk for humans is unknown. Samka is contraindicated during pregnancy.

Breastfeeding: The potential risk for humans is unknown. Samka is contraindicated during breast-feeding.

Fertility: Studies in animals showed effects on fertility. The potential risk for humans is unknown.

Effects on ability to drive and use machines

Has no or negligible influence on the ability to drive or use machines.

Un desirable effects

Immune system disorders: Anaphylactic shock, Generalised rash.

Metabolism and nutrition disorders: Polydipsia, Dehydration, Hyperkalemia, Hyperglycemia, Hypoglycemia, Hyponatremia, Hyperuricemia, Decreased appetite

Nervous system disorders: Syncope, Headache, Dizziness

Vascular disorders: Orthostatic hypotension

Gastrointestinal disorders: Nausea Constipation, Diarrhoea, Dry mouth

Skin and subcutaneous tissue disorders: Ecchymosis, Pruritus Pruritic rash

Renal and urinary disorders: Pollakiuria, Polyuria Renal impairment

General disorders and administration site conditions: Thirst Asthenia, Pyrexia, Malaise

Hepatobiliary disorders: Hepatic disorders, Acute hepatic failure

Investigations: Blood urine present, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics, vasopressin antagonists.

Mechanism of action

Tolvaptan is a selective vasopressin V2-receptor antagonist that specifically blocks the

binding of arginine vasopressin (AVP) at the V2-receptor of the distal portions of the nephron. Tolvaptan affinity for the human V2-receptor is 1.8-times that of native AVP.

Pharmacokinetic properties

Absorption: After oral administration, tolvaptan is rapidly absorbed with peak plasma concentrations occurring about 2 hours after dosing. The absolute bioavailability of tolvaptan is about 56 %.

Distribution: Tolvaptan binds reversibly (98 %) to plasma proteins

Biotransformation: Tolvaptan is extensively metabolised by the liver. Less than 1 % of intact active substance is excreted unchanged in the urine.

Elimination: The terminal elimination half-life is about 8 hours and steady-state concentrations of tolvaptan are obtained after the first dose.

Overdose

There is no specific antidote for tolvaptan intoxication.

Signs and symptoms: 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 (profuse and prolonged aquaresis).

Management: In patients with suspected tolvaptan overdose, assessment of vital signs, electrolyte concentrations, ECG and fluid status is recommended. Appropriate replacement of water and/or electrolytes must continue until aquaresis abates. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (>98 %).

STORAGE:

Protect from heat sunlight & moisture.

All medicines should be kept out of the reach of children.

Store below 30 °C.

خوراک: ڈاکٹریک ہدایت کے مطابق استعمال کریں۔

ہدایات: روشنی، نمی اور گرمی سے محفوظ رکھیں۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔



Manufactured by:

GENOME PHARMACEUTICALS (PVT.) LTD.

Plot # 16/1, Phase IV, Industrial Estate Hattar-Pakistan.

