

## **1. NAME OF THE MEDICINAL PRODUCT**

Samsca 15 mg tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 15 mg tolvaptan.

Excipients:

Each tablet contains approximately 37 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Tablet

Blue, triangular, shallow-convex, debossed with “OTSUKA” and “15” on one side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

### **4.2 Posology and method of administration**

Due to the need for a dose titration phase with close monitoring of serum sodium and volume status, treatment with Samsca should be initiated in hospital.

#### *Posology*

Treatment with tolvaptan should 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. During titration, patients should be monitored for serum sodium and volume status (see section 4.4). In case of inadequate improvement in serum sodium levels, other treatment options should be considered, either in place of or in addition to tolvaptan. For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels should be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatraemia, the treatment duration is determined by the underlying disease and its treatment. Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatraemia is no longer a clinical issue.

#### *Patients with renal impairment*

Tolvaptan is contraindicated in anuric patients (see section 4.3).

Tolvaptan has not been studied in patients with severe renal failure. The efficacy and safety in this population is not well established.

Based on the data available, no dose adjustment is required in those with mild to moderate renal impairment.

#### *Patients with hepatic impairment*

No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). No information is available in patients with severe hepatic impairment (Child-Pugh class C). In these patients dosing should be managed cautiously and electrolytes and volume status should be monitored (see section 4.4).

#### *Elderly population*

No dose adjustment is needed in elderly patients.

#### *Paediatric population*

There is no experience in children and adolescents under the age of 18 years. Samsca is not recommended in the paediatric age group.

#### Method of administration

For oral use.

Administration preferably in the morning, without regard to meals. Tablets should be swallowed without chewing with a glass of water. Samsca should not be taken with grapefruit juice (see section 4.5).

### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients
- Anuria
- Volume depletion
- Hypovolaemic hyponatraemia
- Hypernatraemia
- Patients who cannot perceive thirst
- Pregnancy (see section 4.6)
- Breastfeeding (see section 4.6)

### **4.4 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 should be considered.

#### *Access to water*

Tolvaptan may cause undesirable effects related to water loss such as thirst, dry mouth and dehydration (see section 4.8). Therefore, patients should have access to water and be able to drink sufficient amounts of water. If fluid restricted patients are treated with tolvaptan, extra caution should be exercised to ensure that patients do not become overly dehydrated.

#### *Urinary outflow obstruction*

Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention.

#### *Fluid and electrolyte balance*

Tolvaptan may cause rapid increases in serum sodium. Therefore after initiation of treatment, patients should be closely monitored for serum sodium and volume status. The rate of sodium correction should be

managed carefully in patients at risk for demyelination syndromes (e.g. hypoxia, alcoholism, malnutrition). Fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment. In patients receiving tolvaptan who develop too rapid a rise in serum sodium (>12 mmol/l per 24 hours), treatment with tolvaptan should be discontinued and administration of hypotonic fluid should be considered.

#### *Diabetes mellitus*

Diabetic patients with an elevated glucose concentration (e.g. in excess of 300 mg/dl) may present with pseudohyponatraemia. This condition should be excluded prior and during treatment with tolvaptan. Tolvaptan may cause hyperglycaemia (see section 4.8). Therefore, diabetic patients treated with tolvaptan should be managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes.

#### *Lactose and galactose intolerance*

Samsca contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### *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. Caution should be exercised in co-administering CYP3A4 inhibitors (e.g. ketoconazole, macrolide antibiotics, diltiazem) with tolvaptan (see section 4.4).

Co-administration of grapefruit juice and tolvaptan resulted in a 1.8-fold increase in exposure to tolvaptan. Patients taking tolvaptan should avoid ingesting grapefruit juice.

#### *CYP3A4 inducers*

Tolvaptan plasma concentrations have been decreased by up to 87% (AUC) after the administration of CYP3A4 inducers. Caution should be exercised in co-administering CYP3A4 inducers (e.g. rifampicin, barbiturates) with tolvaptan.

#### *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). Tolvaptan increased plasma levels of lovastatin by 1.3 to 1.5-fold. Even though this increase has no clinical relevance, it indicates tolvaptan can potentially increase exposure to CYP3A4 substrates.

#### *Diuretics*

There is no evidence of clinically significant interactions with loop and thiazide diuretics.

#### *Digoxin*

Steady state digoxin concentrations have been increased (1.3-fold increase in maximum observed plasma concentration [ $C_{max}$ ] and 1.2-fold increase in area under the plasma concentration-time curve over the dosing interval [ $AUC_{\tau}$ ]) when co administered with multiple once daily 60 mg doses of tolvaptan. Patients receiving digoxin should therefore be evaluated for excessive digoxin effects when treated with tolvaptan.

#### *Warfarin*

There is no evidence of clinically significant interactions with warfarin.

#### *Co-administration with hypertonic saline*

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

### **4.6 Pregnancy and lactation**

#### *Pregnancy*

There are no adequate data from the use of tolvaptan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential should use adequate contraceptive measures during tolvaptan use. Samsca must not be used during pregnancy (see section 4.3).

#### *Breastfeeding*

It is unknown whether tolvaptan is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan in breast milk.

The potential risk for humans is unknown. Samsca is contraindicated during breastfeeding (see section 4.3).

### **4.7 Effects on ability to drive and use machines**

When driving vehicles or using machines it should be taken into account that occasionally dizziness, asthenia or syncope may occur.

### **4.8 Undesirable effects**

The adverse reaction profile of tolvaptan is based on a clinical trials database of 3294 tolvaptan-treated patients and is consistent with the pharmacology of the active substance. The frequencies correspond with very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ) and uncommon ( $\geq 1/1000$  to  $< 1/100$ ). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

#### *Adverse reactions reported in clinical trials in patients with hyponatraemia*

The pharmacodynamically predictable and most commonly reported adverse reactions are thirst, dry mouth and pollakiuria occurring in approximately 18%, 9% and 6% of patients.

<b>System Organ Class</b>	<b>Frequency</b>
Metabolism and nutrition disorders	Common: polydipsia, dehydration, hyperkalaemia, hyperglycaemia, decreased appetite
Nervous system disorders	Uncommon: dysgeusia
Vascular disorders	Common: orthostatic hypotension
Gastrointestinal disorders	Very common: nausea Common: constipation, dry mouth
Skin and subcutaneous tissue disorders	Common: ecchymosis, pruritus
Renal and urinary disorders	Common: pollakiuria, polyuria
General disorders and administration site conditions	Very common: thirst Common: asthenia, pyrexia
Investigations	Common: increased blood creatinine

In clinical trials investigating other indications the following undesirable effects have been observed:  
Common: hypernatraemia, hypoglycaemia, hyperuricaemia, syncope, dizziness, headache, malaise, diarrhoea, blood urine present.  
Uncommon: pruritic rash.

#### **4.9 Overdose**

No case of overdose has been reported. Single doses up to 480 mg and multiple doses up to 300 mg per day for 5 days have been well tolerated in clinical trials in healthy volunteers.

The oral median lethal dose (LD<sub>50</sub>) 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.

A profuse and prolonged aquaresis (free water clearance) is anticipated. Adequate fluid intake must be maintained.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Vasopressin antagonists, ATC code C03XA01

Tolvaptan is a selective vasopressin V<sub>2</sub>-receptor antagonist with an affinity for the V<sub>2</sub>-receptor greater than that of native arginine vasopressin. When taken orally, 15 to 60 mg doses of tolvaptan cause an increase in urine excretion resulting in increased aquaresis, decreased urine osmolality and increased serum sodium concentrations. Urine excretion of sodium and potassium are not significantly affected. Tolvaptan metabolites do not appear to have relevant pharmacological activity at clinical concentrations in humans.

Oral administration of 15 to 120 mg doses of tolvaptan produced a significant increase in urine excretion rate within 2 hours of dosing. The increase in 24-hour urine volume was dose dependent. Following single oral doses of 15 to 60 mg, urine excretion rates returned to baseline levels after 24 hours. A mean of about 7 litres was excreted during 0 to 12 hours, independent of dose. Markedly higher doses of tolvaptan produce more sustained responses without affecting the magnitude of excretion, as active concentrations of tolvaptan are present for longer periods of time.

#### *Hyponatraemia*

In 2 pivotal, double-blind, placebo-controlled, clinical trials, a total of 424 patients with euvolaemic or hypervolaemic hyponatraemia (serum sodium <135 mEq/l) due to a variety of underlying causes (heart failure [HF], liver cirrhosis, SIADH and others) were treated for 30 days with tolvaptan (n=216) or placebo (n=208) at an initial dose of 15 mg/day. The dose could be increased to 30 and 60 mg/day depending on response using a 3 day titration scheme. The mean serum sodium concentration at trial entry was 129 mEq/l (range 114 - 136).

The primary endpoint for these trials was the average daily AUC for change in serum sodium from baseline to Day 4 and baseline to Day 30. Tolvaptan was superior to placebo (p<0.0001) for both periods in both studies. This effect was seen in all patients, the severe (serum sodium: < 130 mEq/l) and mild (serum sodium: 130 - < 135 mEq/l) subsets and for all disease aetiology subsets (e.g. HF, cirrhosis,

SIADH/other). At 7 days after discontinuing treatment, sodium values decreased to levels of placebo treated patients.

Following 3 days of treatment, the pooled analysis of the two trials revealed five-fold more tolvaptan than placebo patients achieved normalisation of serum sodium concentrations (49% vs. 11%). This effect continued as on Day 30, when more tolvaptan than placebo patients still had normal concentrations (60% vs. 27%). These responses were seen in patients independent of the underlying disease. The results of self-assessed health status using the SF-12 Health Survey for the mental scores showed statistically significant and clinically relevant improvements for tolvaptan treatment compared to placebo.

Data on the long-term safety and efficacy of tolvaptan were assessed for up to 106 weeks in a clinical trial in patients (any aetiology) who had previously completed one of the pivotal hyponatraemia trials. A total of 111 patients started tolvaptan treatment in an open-label, extension trial, regardless of their previous randomisation. Improvements in serum sodium levels were observed as early as the first day after dosing and continued for on-treatment assessments up to Week 106. When treatment was discontinued, serum sodium concentrations decreased to approximately baseline values, despite the reinstatement of standard care therapy.

#### *Clinical data from trials in other patient populations*

EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) was a long-term outcome, double-blind, controlled clinical trial in patients hospitalised with worsening HF and signs and symptoms of volume overload. In the long-term outcome trial, a total of 2072 patients received 30 mg tolvaptan with standard of care (SC) and 2061 received placebo with SC. The primary objective of the study was to compare the effects of tolvaptan + SC with placebo + SC on the time to all-cause mortality and on the time to first occurrence of cardiovascular (CV) mortality or hospitalisation for HF. Tolvaptan treatment had no statistically significant favourable or unfavourable effects on overall survival or the combined endpoint of CV mortality or HF hospitalisation, and did not provide convincing evidence for clinically relevant benefit.

## **5.2 Pharmacokinetic properties**

### *Absorption and distribution*

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%. Co-administration with food has no effect on plasma concentrations. Following single oral doses of  $\geq 300$  mg, peak plasma concentrations appear to plateau, possibly due to saturation of absorption. The terminal elimination half-life is about 8 hours and steady-state concentrations of tolvaptan are obtained after the first dose. Tolvaptan binds reversibly (98%) to plasma proteins.

### *Biotransformation and elimination*

Tolvaptan is extensively metabolised by the liver. Less than 1% of intact active substance is excreted unchanged in the urine. Radio labelled tolvaptan experiments showed that 40% of the radioactivity was recovered in the urine and 59% was recovered in the faeces where unchanged tolvaptan accounted for 32% of radioactivity. Tolvaptan is only a minor component in plasma (3%).

### *Linearity*

Tolvaptan has linear pharmacokinetics for doses of 15 to 60 mg.

### *Pharmacokinetics in special populations*

Clearance of tolvaptan is not significantly affected by age.

The effect of mildly or moderately impaired hepatic function (Child-Pugh classes A and B) on the pharmacokinetics of tolvaptan was investigated in 87 patients with liver disease of various origins. No clinically significant changes have been seen in clearance for doses ranging from 5 to 60 mg. Very limited information is available in patients with severe hepatic impairment (Child-Pugh class C).

In a population pharmacokinetic analysis in patients with hepatic edema, AUC of tolvaptan in severely (Child-Pugh class C) and mildly or moderately (Child-Pugh classes A and B) hepatic impaired patients were 3.1 and 2.3 times higher than that in healthy subjects.

In an analysis on population pharmacokinetics for patients with heart failure, tolvaptan concentrations of patients with mildly (creatinine clearance [ $C_{cr}$ ] 50 to 80 ml/min) or moderately ( $C_{cr}$  20 to 50 ml/min) impaired renal function were not significantly different to tolvaptan concentrations in patients with normal renal function ( $C_{cr}$  80 to 150 ml/min). The efficacy and safety of tolvaptan in those with a creatinine clearance <10 ml/min has not been evaluated and is therefore unknown.

### **5.3 Preclinical safety data**

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential.

Teratogenicity was noted in rabbits given 1000 mg/kg/day (15 times the exposure from the recommended human dose on an AUC basis). No teratogenic effects were seen in rabbits at 300 mg/kg/day (about 2.5 to 5.3 times the exposure in humans at the recommended dose, based on AUC).

In a peri- and post-natal study in rats, delayed ossification and reduced pup bodyweight were seen at the high dose of 1000 mg/kg/day.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Maize starch  
Hydroxypropylcellulose  
Lactose monohydrate  
Magnesium stearate  
Microcrystalline cellulose  
Indigo carmine (E 132) aluminium lake

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

4 years

### **6.4 Special precautions for storage**

Store in the original package in order to protect from light and moisture.

#### **6.5 Nature and contents of container**

10 x 1 tablets in PVC/aluminium perforated unit dose blister.  
30 x 1 tablets in PVC/aluminium perforated unit dose blister.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

No special requirements.

### **7. MARKETING AUTHORISATION HOLDER**

Otsuka Pharmaceutical Europe Ltd  
Hunton House  
Highbridge Business Park  
Oxford Road  
Uxbridge  
Middlesex, UB8 1HU  
United Kingdom

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/09/539/001-002

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 03/08/2009

### **10. DATE OF REVISION OF THE TEXT**

08/2011

Detailed information on this product is available on the website of the European Medicines Agency  
<http://www.ema.europa.eu>