ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Samsca 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg tolvaptan.

Excipient with known effect:
Each tablet contains approximately 35 mg lactose (as monohydrate).

For the 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 (see section 4.4), 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. Use of tolvaptan in combination with other options may increase the risk of overly rapid correction of serum sodium (see sections 4.4 and 4.5). 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.
Samsca should not be taken with grapefruit juice (see section 4.5).

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 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).No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).

Elderly population
No dose adjustment is needed in elderly patients.

Paediatric population
The safety and efficacy of tolvaptan in children and adolescents under the age of 18 years have not yet been established. 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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 adverse reactions 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.

Dehydration
Volume status should be monitored in patients taking tolvaptan because treatment with tolvaptan may result in severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of tolvaptan and increase fluid intake.

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
Fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment. Administration of tolvaptan may cause too rapid increases in serum sodium (≥ 12 mmol/l per 24 hours, please see below); therefore, monitoring of serum sodium in all patients should start no later than 4-6 hours after treatment initiation. During the first 1-2 days and until the tolvaptan dose is stabilised serum sodium and volume status should be monitored at least every 6 hours.

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.
Too rapid correction of hyponatraemia (increase ≥ 12 mmol/l/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. Therefore after initiation of treatment, patients should be closely monitored for serum sodium and volume status (see above).
In order to minimise the risk of too rapid correction of hyponatraemia the increase of serum sodium should be less than 10-12 mmol/l/24 hours and less than 18 mmol/l/48 hours. Therefore, more precautionary limits apply during the early treatment phase.
If sodium correction exceeds 6 mmol/l during the first 6 hours of administration or 8 mmol/l during the first 6-12 hours, respectively, the possibility that serum sodium correction may be overly rapid should be considered. These patients should be monitored more frequently regarding their serum sodium and administration of hypotonic fluid is recommended. In case serum sodium increases ≥ 12 mmol/l within 24 hours or ≥ 18 mmol/l within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid.
In patients at higher risk of demyelination syndromes, for example those with hypoxia, alcoholism or malnutrition, the appropriate rate of sodium correction may be lower than that in patients without risk factors; these patients should be very carefully managed.

Patients who received other treatment for hyponatraemia or medicinal products which increase serum sodium concentration (see section 4.5) prior to initiation of treatment with Samsca should be managed very cautiously. These patients may be at higher risk for developing rapid correction of serum sodium during the first 1-2 days of treatment due to potential additive effects.
Co-administration of Samsca with other treatments for hyponatraemia, and medications that increase serum sodium concentration, is not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations (see section 4.5).

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.

Hepatotoxicity
Drug induced liver injury has been observed in clinical trials investigating a different potential indication (autosomal dominant polycystic kidney disease) with long-term use of tolvaptan at higher doses than for the approved indication (see section 4.8).
In these clinical trials, clinically significant increases (greater than 3 x Upper Limit of Normal) in serum alanine aminotransferase (ALT), along with clinically significant increases (greater than 2 x Upper Limit of Normal) in serum total bilirubin were observed in 3 patients treated with tolvaptan. In addition, an increased incidence of significant elevations of ALT was observed in patients treated with tolvaptan [4.4% (42/958)] compared to those receiving placebo [1.0% (5/484)]. Elevation (>3xULN) of serum aspartate aminotransferase (AST) was observed in 3.1% (30/958) of patients on tolvaptan and 0.8% (4/484) patients on placebo. Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. The elevations gradually improved after

discontinuation of tolvaptan. These findings may suggest that tolvaptan has the potential to cause irreversible and potentially fatal liver injury.

Liver function tests should be promptly performed in patients taking tolvaptan who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If liver injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine the probable cause. Tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

Anaphylaxis
In post-marketing experience, anaphylaxis (including anaphylactic shock and generalised rash) has been reported very rarely following administration of Samsca. Patients should be carefully monitored during treatment. If an anaphylactic reaction or other serious allergic reactions occur, administration of Samsca should be discontinued immediately and appropriate therapy initiated.

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

Co-administration with other treatments for hyponatraemia and medicinal products that increase serum sodium concentration
There is no experience from controlled clinical trials with concomitant use of Samsca and other treatments for hyponatraemia such as hypertonic saline, oral sodium formulations, and medicinal products that increase serum sodium concentration. Medicinal products with high sodium content such as effervescent analgesic preparations and certain sodium containing treatments for dyspepsia may also increase serum sodium concentration. Concomitant use of Samsca with other treatments for hyponatraemia or other medicinal products that increase serum sodium concentration may result in a higher risk for developing rapid correction of serum sodium (see section 4.4) and is therefore 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 (see section 4.4).

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
While there does not appear to be a synergistic or additive effect of 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. If dehydration or renal dysfunction becomes evident, take appropriate action which may include the need to interrupt or reduce doses of tolvaptan and/or diuretics, increase fluid intake, evaluate and address other potential causes of renal dysfunction or dehydration.

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_{τ}]) 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.

Co-administration with vasopressin analogues
In addition to its renal aquaretic effect, tolvaptan is capable of blocking vascular vasopressin V2 receptors involved in the release of coagulation factors (e.g., von Willebrand factor) from endothelial cells. Therefore, the effect of vasopressin analogues such as desmopressin may be attenuated in patients using such analogues to prevent or control bleeding when co-administered with tolvaptan.

4.6 Fertility, 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.
Samsca must not be used during pregnancy (see section 4.3).

Women of childbearing potential
Women of childbearing potential should use adequate contraceptive measures during tolvaptan use.

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).

Fertility
Two fertility studies in rats showed effects on the parental generation (decreased food consumption and body weight gain, salivation), but tolvaptan did not affect reproductive performance in males and there were no effects on the foetuses. In females, abnormal oestrus cycles were seen in both studies. The no observed adverse effect level (NOAEL) for effects on reproduction in females (100 mg/kg/day) was about 16-times the maximum human recommended dose on a mg/m^2 basis.

4.7 Effects on ability to drive and use machines

Samsca has no or negligible influence on the ability to drive or use machines. However, when driving vehicles or using machines it should be taken into account that occasionally dizziness, asthenia or syncope may occur.

4.8 Undesirable effects

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

Tabulated list of adverse reactions
The frequencies of the adverse reactions correspond with very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Frequency**			
	Very common	Common	Uncommon	Not known
Immune system disorders				anaphylactic shock, generalised rash
Metabolism and nutrition disorders		polydipsia, dehydration, hyperkalaemia, hyperglycaemia, decreased appetite		
Nervous system disorders			dysgeusia	
Vascular disorders		orthostatic hypotension		
Gastrointestinal disorders	nausea	constipation, dry mouth		
Skin and subcutaneous tissue disorders		ecchymosis, pruritus		
Renal and urinary disorders		pollakiuria, polyuria	renal impairment	
General disorders and administration site conditions	thirst	asthenia, pyrexia		
Investigations		increased blood creatinine		
Surgical and medical procedures		rapid correction of hyponatraemia, sometimes leading to neurological symptoms		

In clinical trials investigating other indications the following undesirable effects have been observed:
Common: alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), hypernatraemia, hypoglycaemia, hyperuricaemia, syncope, dizziness, headache, malaise, diarrhoea, blood urine present.
Uncommon: bilirubin increased (see section 4.4), pruritic rash.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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_{50}) 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: Diuretics, vasopressin antagonists, ATC code C03XA01

Tolvaptan is a selective vasopressin V_2-receptor antagonist with an affinity for the V_2-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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Samsca in one or more subsets of the paediatric population in treatment of dilutional hyponatraemia (see section 4.2 for information on paediatric use).

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 ≥ 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 reveal 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
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
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
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Samsca 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg tolvaptan.

Excipient with known effect:
Each tablet contains approximately 70 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

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4.2 Posology and method of administration

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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. Use of tolvaptan in combination with other options may increase the risk of overly rapid correction of serum sodium (see sections 4.4 and 4.5). 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.
Samsca should not be taken with grapefruit juice (see section 4.5).

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Tolvaptan has not been studied in patients with severe renal failure. The efficacy and safety in this population is not well established.
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Patients with hepatic impairment
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Elderly population
No dose adjustment is needed in elderly patients.

Paediatric population
The safety and efficacy of tolvaptan in children and adolescents under the age of 18 years have not yet been established. 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Anuria
- Volume depletion
- Hypovolaemic hyponatraemia
- Hypernatraemia
- Patients who cannot perceive thirst
- Pregnancy (see section 4.6)
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Urinary outflow obstruction
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If sodium correction exceeds 6 mmol/l during the first 6 hours of administration or 8 mmol/l during the first 6-12 hours, respectively, the possibility that serum sodium correction may be overly rapid should be considered. These patients should be monitored more frequently regarding their serum sodium and administration of hypotonic fluid is recommended. In case serum sodium increases ≥ 12 mmol/l within 24 hours or ≥ 18 mmol/l within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid.
In patients at higher risk of demyelination syndromes, for example those with hypoxia, alcoholism or malnutrition, the appropriate rate of sodium correction may be lower than that in patients without risk factors; these patients should be very carefully managed.

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Drug induced liver injury has been observed in clinical trials investigating a different potential indication (autosomal dominant polycystic kidney disease) with long-term use of tolvaptan at higher doses than for the approved indication (see section 4.8).
In these clinical trials, clinically significant increases (greater than 3 x Upper Limit of Normal) in serum alanine aminotransferase (ALT), along with clinically significant increases (greater than 2 x Upper Limit of Normal) in serum total bilirubin were observed in 3 patients treated with tolvaptan. In addition, an increased incidence of significant elevations of ALT was observed in patients treated with tolvaptan [4.4% (42/958)] compared to those receiving placebo [1.0% (5/484)]. Elevation (>3xULN) of serum aspartate aminotransferase (AST) was observed in 3.1% (30/958) of patients on tolvaptan and 0.8% (4/484) patients on placebo. Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. The elevations gradually improved after

discontinuation of tolvaptan. These findings may suggest that tolvaptan has the potential to cause irreversible and potentially fatal liver injury.

Liver function tests should be promptly performed in patients taking tolvaptan who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If liver injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine the probable cause. Tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

Anaphylaxis
In post-marketing experience, anaphylaxis (including anaphylactic shock and generalised rash) has been reported very rarely following administration of Samsca. Patients should be carefully monitored during treatment. If an anaphylactic reaction or other serious allergic reactions occur, administration of Samsca should be discontinued immediately and appropriate therapy initiated.

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

Co-administration with other treatments for hyponatraemia and medicinal products that increase serum sodium concentration
There is no experience from controlled clinical trials with concomitant use of Samsca and other treatments for hyponatraemia such as hypertonic saline, oral sodium formulations, and medicinal products that increase serum sodium concentration. Medicinal products with high sodium content such as effervescent analgesic preparations and certain sodium containing treatments for dyspepsia may also increase serum sodium concentration. Concomitant use of Samsca with other treatments for hyponatraemia or other medicinal products that increase serum sodium concentration may result in a higher risk for developing rapid correction of serum sodium (see section 4.4) and is therefore 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 (see section 4.4).

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
While there does not appear to be a synergistic or additive effect of 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. If dehydration or renal dysfunction becomes evident, take appropriate action which may include the need to interrupt or reduce doses of tolvaptan and/or diuretics, increase fluid intake, evaluate and address other potential causes of renal dysfunction or dehydration.

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_{τ}]) 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.

Co-administration with vasopressin analogues
In addition to its renal aquaretic effect, tolvaptan is capable of blocking vascular vasopressin V2 receptors involved in the release of coagulation factors (e.g., von Willebrand factor) from endothelial cells. Therefore, the effect of vasopressin analogues such as desmopressin may be attenuated in patients using such analogues to prevent or control bleeding when co-administered with tolvaptan.

4.6 Fertility, 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.
Samsca must not be used during pregnancy (see section 4.3).

Women of childbearing potential
Women of childbearing potential should use adequate contraceptive measures during tolvaptan use.

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).

Fertility
Two fertility studies in rats showed effects on the parental generation (decreased food consumption and body weight gain, salivation), but tolvaptan did not affect reproductive performance in males and there were no effects on the foetuses. In females, abnormal oestrus cycles were seen in both studies. The no observed adverse effect level (NOAEL) for effects on reproduction in females (100 mg/kg/day) was about 16-times the maximum human recommended dose on a mg/m^2 basis.

4.7 Effects on ability to drive and use machines

Samsca has no or negligible influence on the ability to drive or use machines. However, when driving vehicles or using machines it should be taken into account that occasionally dizziness, asthenia or syncope may occur.

4.8 Undesirable effects

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

Tabulated list of adverse reactions
The frequencies of the adverse reactions correspond with very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Frequency**			
	Very common	Common	Uncommon	Not known
Immune system disorders				anaphylactic shock, generalised rash
Metabolism and nutrition disorders		polydipsia, dehydration, hyperkalaemia, hyperglycaemia, decreased appetite		
Nervous system disorders			dysgeusia	
Vascular disorders		orthostatic hypotension		
Gastrointestinal disorders	nausea	constipation, dry mouth		
Skin and subcutaneous tissue disorders		ecchymosis, pruritus		
Renal and urinary disorders		pollakiuria, polyuria	renal impairment	
General disorders and administration site conditions	thirst	asthenia, pyrexia		
Investigations		increased blood creatinine		
Surgical and medical procedures		rapid correction of hyponatraemia, sometimes leading to neurological symptoms		

In clinical trials investigating other indications the following undesirable effects have been observed:
Common: alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), hypernatraemia, hypoglycaemia, hyperuricaemia, syncope, dizziness, headache, malaise, diarrhoea, blood urine present.
Uncommon: bilirubin increased (see section 4.4), pruritic rash.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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_{50}) 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: Diuretics, vasopressin antagonists, ATC code C03XA01

Tolvaptan is a selective vasopressin V_2-receptor antagonist with an affinity for the V_2-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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Samsca in one or more subsets of the paediatric population in treatment of dilutional hyponatraemia (see section 4.2 for information on paediatric use).

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 ≥ 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 reveal 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
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/539/003-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03/08/2009
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AndersonBrecon (UK) Ltd.
Wye Valley Business Park
Brecon Road
Hay-on-Wye
Hereford, HR3 5PG
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Samsca 15 mg tablets
tolvaptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg tolvaptan.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/539/001 10 tablets
EU/1/09/539/002 30 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Samsca 15 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Samsca 15 mg tablets
tolvaptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Samsca 30 mg tablets
tolvaptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg tolvaptan.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/539/003 10 tablets
EU/1/09/539/004 30 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Samsca 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Samsca 30 mg tablets
tolvaptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Samsca 15 mg tablets
Samsca 30 mg tablets
tolvaptan

Read all of this leaflet carefully before you start taking 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, please 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 symptoms 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 4.

In this leaflet:

1. What Samsca is and what it is used for

Samsca, which contains the active substance tolvaptan, belongs to a group of medicines called vasopressin antagonists. Vasopression is a hormone that helps prevent the loss of water from the body by reducing urine output. Antagonist means that it prevents vasopressin having its effect on water retention. This leads to a reduction in the amount of water in the body by increasing urine production and as a result it increases the level or concentration of sodium in your blood.

Samsca is used to treat low serum sodium levels in adults. You have been prescribed Samsca because you have a lowered sodium level in your blood as a result of a disease called “syndrome of inappropriate antidiuretic hormone secretion” (SIADH) where the kidneys retain too much water. This disease causes an inappropriate production of the hormone vasopressin which has caused the sodium levels in your blood to get too low (hyponatraemia). That can lead to difficulties in concentration and memory, or in keeping your balance.

2. What you need to know before you take Samsca

<u>Do not</u> take Samsca

- if you are allergic to tolvaptan or any of the other ingredients of this medicine (listed in section 6)
- if your kidneys do not work (no urine production)
- if you have a condition which increases the salt in your blood (“hypernatraemia”)
- if you have a condition which is associated with a very low blood volume
- if you do not realise when you are thirsty
- if you are pregnant
- if you are breastfeeding.

Warnings and precautions

Talk to your doctor or pharmacist before taking Samsca:

- if you cannot drink enough water or if you are fluid restricted
- if you have difficulties in urination or have an enlarged prostate
- if you suffer from liver disease
- if you have diabetes.

Drinking enough water
Samsca causes water loss because it increases your urine production. This water loss may result in side effects such as dry mouth and thirst or even more severe side effects like kidney problems (see section 4). It is therefore important that you have access to water and that you are able to drink sufficient amounts when you feel thirsty.

Children and adolescents
Samsca is not suitable for children and adolescents (under age 18).

Other medicines and Samsca

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Products containing ketoconazole (against fungal infections), macrolide antibiotics, or diltiazem (treatment for high blood pressure and chest pain) may increase the effects of Samsca. Samsca may increase the effect of digoxin (used for treatment of irregularities of heart beat and heart failure). Barbiturates (used to treat epilepsy/seizures and some sleep disorders) or rifampicin (against tuberculosis) may decrease the effects of Samsca.

Other products which increase the salt in your blood or which contain large amounts of salt may increase the effects of Samsca. Medicines which also increase your urine production (diuretics) may further increase the risk of water loss related side effects (see "Drinking enough water" above). Therefore, please tell your doctor about all medicines you are receiving or have recently received, including medicines obtained without a prescription.

Samsca may reduce the effect of desmopressin (used to increase blood clotting factors).

It may still be alright for you to take these medicines and Samsca together. Your doctor will be able to decide what is suitable for you.

Samsca with food and drink

- Avoid drinking grapefruit juice when taking Samsca.

Pregnancy and breastfeeding

Pregnant women **must not** take this medicine.
Breastfeeding women **must not** take this medicine.

Women of childbearing potential should use adequate contraceptive measures during use of this medicine.

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Samsca is unlikely to adversely affect your ability to drive a car or to operate machinery. However, you may occasionally feel dizzy or weak or you may faint for a short period.

Samsca contains lactose.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Samsca

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

- Treatment with Samsca will be initiated in hospital
- For treatment of your low sodium (hyponatraemia), the dose can be from 15 mg to 60 mg once a day. Your doctor will start with a dose of 15 mg and may then increase it to a maximum of 60 mg to achieve the desired level of serum sodium. To monitor the effects of Samsca your doctor will do regular blood tests.
- Swallow the tablet without chewing, with a glass of water.
- Take the tablets once a day preferably in the morning with or without food.

If you take more Samsca than you should

If you have taken more tablets than your prescribed dose, **drink plenty of water and contact your doctor or your local hospital immediately**. Remember to take the medicine pack with you so that it is clear what you have taken.

If you forget to take Samsca

If you forget to take your medicine you should take the dose as soon as you remember on the same day. If you do not take your tablet on one day, take your normal dose on the next day. **DO NOT** take a double dose to make up for a forgotten dose.

If you stop taking Samsca

If you stop taking Samsca this may lead to reoccurrence of your low sodium. Therefore, you should only stop taking Samsca if you notice side effects requiring urgent medical attention (see section 4) or if your doctor tells you to.

If you have further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

If you notice any of the following side effects, you may need urgent medical attention. Stop taking Samsca and immediately contact a doctor or go to the nearest hospital if you:

- find it difficult to urinate
- find a swelling of the face, lips or tongue, itching, generalised rash, or severe wheezing or breathlessness (symptoms of an allergic reaction).

Consult your doctor if symptoms of fatigue, loss of appetite, right upper abdominal discomfort, dark urine or jaundice (yellowing of skin or eyes) occur.

Other side effects

Very common (may affect more than 1 in 10 people)
- thirst
- nausea

Common (may affect up to 1 in 10 people)
- raised levels of liver enzymes in the blood
- dry mouth
- excessive drinking of water
- increased need to urinate, or to urinate more frequently
- water loss
- tiredness, general weakness
- decreased appetite
- constipation
- dizziness
- low blood pressure when standing up
- fainting
- patchy bleeding in the skin
- itching
- fever
- high levels of sodium, potassium, creatinine, uric acid and blood sugar
- rapid rise in level of sodium
- decrease in level of blood sugar
- headache
- general feeling of being unwell
- diarrhoea
- blood in urine

Uncommon (may affect up to 1 in 100 people)
- increase of bilirubin in the blood
- kidney problems
- sense of taste altered
- itchy rash

Not known
Other side effects have occurred in a very small number of people but their exact frequency is unknown.
- allergic reactions (see above)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Samsca

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Samsca contains

The active substance is tolvaptan.
Each Samsca 15 mg tablet contains 15 mg tolvaptan.
Each Samsca 30 mg tablet contains 30 mg tolvaptan.

The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropylcellulose, magnesium stearate, indigo carmine (E 132) aluminium lake.

What Samsca looks like and contents of the pack

Samsca 15 mg is a blue, triangular, convex tablet, with “OTSUKA” and “15” on one side.
Samsca 30 mg is a blue, round, convex tablet, with “OTSUKA” and “30” on one side.

Your medicine is supplied in perforated unit dose blisters of 10 x 1 tablets. One pack with 10 Samsca tablets contains one blister of 10 tablets and one pack with 30 Samsca tablets contains three blisters of 10 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
United Kingdom

Manufacturer

AndersonBrecon (UK) Ltd.
Wye Valley Business Park
Brecon Road
Hay-on-Wye
Hereford, HR3 5PG
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Otsuka Pharmaceutical Europe Ltd
Tél/Tel: +44 (0)203 747 5000

България
Otsuka Pharmaceutical Europe Ltd
Тел: +44 (0)203 747 5000

Česká republika
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Danmark
Otsuka Pharma Scandinavia AB
Tlf: +46854 528 660

Deutschland
Otsuka Pharma GmbH
Tel: +49691 700 860

Eesti
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Ελλάδα
Otsuka Pharmaceutical Europe Ltd
Τηλ: +44 (0)203 747 5000

España
Otsuka Pharmaceutical S.A
Tel: +3493 2081 020

France
Otsuka Pharmaceutical France SAS
Tél: +33147 080 000

Hrvatska
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Ireland
Otsuka Pharmaceuticals (UK) Ltd
Tel: +44 (0)203 747 5300

Ísland
Otsuka Pharma Scandinavia AB
Tlf: +46854 528 660

Italia
Otsuka Pharmaceutical Italy S.r.l.
Tel: +39 02 00 63 27 10

Κύπρος
Otsuka Pharmaceutical Europe Ltd
Τηλ: +44 (0)203 747 5000

Lietuva
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Luxembourg/Luxemburg
Otsuka Pharmaceutical Europe Ltd
Tel/ Tél: +44 (0)203 747 5000

Magyarország
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Malta
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Nederland
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Norge
Otsuka Pharma Scandinavia AB
Tlf: +46854 528 660

Österreich
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Polska
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Portugal
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

România
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Slovenija
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Slovenská republika
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

Suomi/Finland
Otsuka Pharma Scandinavia AB
Tel/ Puh: +46854 528 660

Sverige
Otsuka Pharma Scandinavia AB
Tel: +46854 528 660

Latvija
Otsuka Pharmaceutical Europe Ltd
Tel: +44 (0)203 747 5000

United Kingdom
Otsuka Pharmaceuticals (UK) Ltd
Tel: +44 (0)203 747 5300

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.