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.

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 demyelinisation 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\text{max}] and 1.2-fold increase in area under the plasma concentration-time curve over the dosing interval [AUC\text{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.

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 (≥1/10), common (≥1/100 to <1/10) and uncommon (≥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.

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<td>Uncommon: dysgeusia</td>
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In clinical trials investigating other indications the following undesirable effects have been observed:

Common: hypernatraemia, hypoglycaemia, hyperuricaemia, syncope, dizziness.

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

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 V2-receptor antagonist with an affinity for the V2-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 aquarexia, 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 ≥ 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 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/0/00/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}>
10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
1. NAME OF THE MEDICINAL PRODUCT

Samsca 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg tolvaptan.

Excipients:
Each tablet contains approximately 74 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
Blue, round, shallow-convex, deossed with “OTSUKA” and “30” 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.

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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
- Hyponatraemia
- Patients who cannot perceive thirst
- Pregnancy (see section 4.6)
- Breastfeeding (see section 4.6)

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

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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.

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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 [Cmax] and 1.2-fold increase in area under the plasma concentration-time curve over the dosing interval [AUCτ]) 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.

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

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5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin antagonists, ATC code C03XA01

Tolvaptan is a selective vasopressin V2-receptor antagonist with an affinity for the V2-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 aquarexis, 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.

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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 ≥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 an analysis on population pharmacokinetics for patients with heart failure, tolvaptan concentrations of patients with mildly (creatinine clearance [Ccr] 50 to 80 ml/min) or moderately (Ccr 20 to 50 ml/min) impaired renal function were not significantly different to tolvaptan concentrations in patients with normal renal function (Ccr 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/0/00/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZAION

<{DD/MM/YYYY}>
10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER
   RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Brecon Pharmaceuticals Ltd.
Wye Valley Business Park
Brecon Road
Hay-on-Wye
Hereford, HR3 5PG
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

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

Not applicable

• OTHER CONDITIONS

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 1.3 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
• When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
• Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
• At the request of the EMEA
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

<table>
<thead>
<tr>
<th>OUTER CARTON</th>
</tr>
</thead>
</table>

#### 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

<table>
<thead>
<tr>
<th>10 tablets</th>
<th>30 tablets</th>
</tr>
</thead>
</table>

#### 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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.
Hunton House
Highbridge Business Park
Oxford Road
Uxbridge
Middlesex, UB8 1HU
UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

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
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTERS</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Samsca 15 mg tablets</td>
</tr>
<tr>
<td>tolvaptan</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>Otsuka</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

#### OUTER CARTON

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Samsca 30 mg tablets</td>
<td></td>
</tr>
<tr>
<td>tolvaptan</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Each tablet contains 30 mg tolvaptan</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
<th></th>
</tr>
</thead>
<tbody>
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<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
<td></td>
</tr>
<tr>
<td>For oral use.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Store in the original package in order to protect from light and moisture.</td>
<td></td>
</tr>
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11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

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
Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. WHAT SAMSCA IS AND WHAT IT IS USED FOR
2. BEFORE YOU TAKE SAMSCA
3. HOW TO TAKE SAMSCA
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE SAMSCA
6. FURTHER INFORMATION

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. This 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 of sodium in your blood.

You have been prescribed Samsca because you have a disease called “syndrome of inappropriate antidiuretic hormone secretion” (SIADH). 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. BEFORE YOU TAKE SAMSCA

**Do not** take Samsca

- if you are allergic to tolvaptan or any of the other ingredients of Samsca (see section 6)
- if your kidneys do not work (no urine production)
- if you have a condition which increases the salt in your blood (“hyponatraemia”)
- 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.

**Take special care with Samsca**

Before taking Samsca tell your doctor:

- 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 (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**

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

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken 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.

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.

**Taking Samsca with food and drink**

• Samsca tablets can be taken with or without food.
• Avoid drinking grapefruit juice when taking Samsca.

**Pregnancy and breastfeeding**

Pregnant women must not take this medicine.
Before taking Samsca you must tell your doctor if you are pregnant, if you think you are pregnant, or if you intend to become pregnant.
Breastfeeding women must not take this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**

Samsca may occasionally make you feel dizzy or weak or you may faint for a short period.

**Important information about some of the ingredients of Samsca**

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

3. **HOW TO TAKE SAMSCA**

• Treatment with Samsca will be initiated in hospital
• Always take Samsca exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
• 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 forgotten individual doses.

**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 product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

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

These side effects may occur with certain frequencies, which are defined as follows:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

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.

**Side effects reported in clinical studies with Samsca were:**

**Very common**

- thirst
- nausea

**Common**

- 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
• rise in levels of sodium, potassium, creatinine, uric acid and blood sugar
• decrease in level of blood sugar

Uncommon
• sense of taste altered
• itchy rash

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SAMSCA

Keep out of the reach and sight of children.

Do not use Samsca 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER 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
Hunton House
Highbridge Business Park
Oxford Road
Uxbridge
Middlesex, UB8 1HU
United Kingdom

Manufacturer

Brecon Pharmaceuticals 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: +441895 207 100

Luxembourg/Luxemburg
Otsuka Pharmaceutical Europe Ltd
Tel/ Tél: +441895 207 100

България
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Magyarország
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Česká republika
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Tel: +49691 700 860

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Tlf: +46854 528 660

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

Portugal
Otsuka Pharmaceutical Europe Ltd
Tel: +441895 207 100
This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMA) website: http://www.emea.europa.eu/.