SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TOLVAT 30 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains tolvaptan 30 mg.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

TOLVAT 30: Light blue colored, round shaped biconvex uncoated uncoted tablets with plain surface on both sides.

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 Tolvat 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 (ChildPugh 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. Tolvat 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. Tolvat should not be taken with grapefruit juice (see section 4.5).

Legal Category: POM

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.

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

Tolvat 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 Tolvat with other treatments for hyponatraemia, and medications that increase serum sodium concentration, is not recommended (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.

Lactose and galactose intolerance

Tolvat 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 timeconcentration 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 [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 other treatments for hyponatraemia and medicinal products that increase serum sodium concentration

There is no experience from controlled clinical trials with concomitant use of Tolvat 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 Tolvat 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.

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 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.

Tolvat 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. Tolvat 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 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.

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

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 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.

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%. Coadministration 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 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

Lactose monohydrate, microcrystalline cellulose, maize starch, low substituted hydroxypropyl cellulose, polysorbate 80, hydroxypropyl methylcellulose, brilliant blue FCF and magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 months.

6.4 Special Precautions for Storage

Do not Store above 30°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and Contents of Container

4 tablets of Tolvaptan Tablets 30 mg are packed in plain aluminium foil on one side and printed aluminum foil on another side in the form of a blister and such a blister pack is further packed in one carton along with the printed literature. and
10 tablets of Tolvaptan Tablets 30 mg are packed in plain aluminium foil on one side and printed aluminum foil on another side in the form of a blister and such a blister pack is further packed in one carton along with the printed literature.

6.6 Special Precautions for Disposal

Any unused product or waste material should be disposed off in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MSN LABORATORIES PRIVATE LIMITED,
MSN House, Plot No.: C-24,
Industrial Estate, Sanath Nagar,
Hyderabad – 500 018 India.

8. MARKETING AUTHORISATION NUMBER

RWANDA FDA-HMP-MA-0012

9. DATE OF FIRST AUTHORISATION

First Authorisation: 5th March,2020

10. DATE OF REVISION OF THE TEXT

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