IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Tolvaptan Ascend 7.5 mg tablets
Tolvaptan
PA23429/006/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Tolvaptan Ascend 7.5mg Tablets, from Ascend GmbH on 10th May 2024

Adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

This decentralised application concerns generic version of Tolvaptan tablets.
Reference product: Samsca 7.5 mg tablets, which was authorized to Otsuka Pharmaceutical Netherlands B.V. on 02/08/2003 in accordance with Article 8(3) of Directive 2001/83/EC.

The legal basis for this submission in IE and other concerned member states is article 10.1 of directive 2001/83/EC as amended.

With IE as the Reference Member State in this Decentralised Procedure, Ascend GmbH
is applying for the Marketing Authorisations for 7.5mg tablets in DE.
The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product:	Tolvaptan Ascend 7.5mg Tablets
Name(s) of the active substance(s) (INN)	Tolvaptan
Pharmacotherapeutic classification (ATC code)	C03XA01
Pharmaceutical form and strength(s)	7.5mg Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA23429/006/001
Marketing Authorisation Holder	Ascend GmbH
MRP/DCP No.	IE/H/1249/001/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Tolvaptan Ascend 7.5mg Tablets.

II.2 Drug substance

The active substance is tolvaptan, an established active substance supported by an ASMF, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each tablet contains 7.5 mg tolvaptan.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Tolvaptan Ascend 7.5 mg tablets,.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Samsca 7.5 mg tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

Not applicable

III.3 Pharmacokinetics

Not applicable

III.4 Toxicology

Not applicable

III.5 Ecotoxicity/environmental risk assessment

Since Tolvaptan Ascend 7.5mg tablet is a generic product, an increase in environmental exposure to the active substance is not anticipated. Environmental risk assessment studies are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Tolvaptan are well known. As Tolvaptan is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

For generic applications (Article 10.1, 10.3, 10.4, 10.c),the following statements can be used:

Tolvaptan is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Samsca 7.5 mg tablets, which was authorized to Otsuka Pharmaceutical Netherlands B.V. on 02/08/2003 in accordance with Article 8(3) of Directive 2001/83/EC.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Tolvaptan Ascend is compared with the pharmacokinetic profile of the reference product Samsca 7.5mg.

Samsca 7.5mg and test tablet tolvaptan ascend are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

An open label, balanced, pivotal, laboratory blind, randomized, two period, two
treatment, two sequence, single dose, two way, crossover, bioequivalence study was performed.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption

After oral administration, tolvaptan is rapidly absorbed with peak plasma concentrations occurring about 2 hours after dosing. The absolute bioavailability of tolvaptan is about 56 %. Co-administration of a 60 mg dose with a high-fat meal increases peak concentrations 1.4-fold with no change in AUC and no change in urine output. Following single oral doses of 300 mg, peak plasma concentrations appear to plateau, possibly due to saturation of absorption.

Distribution

Tolvaptan binds reversibly (98 %) to plasma proteins.
Biotransformation
Tolvaptan is extensively metabolised by the liver. Less than 1 % of intact active substance is excreted unchanged in the urine. In-vitro studies indicate that tolvaptan or its oxobutyric metabolite may have the potential to inhibit OATP1B1, OAT3, BCRP and OCT1 transporters. Administration of rosuvastatin (OATP1B1 substrate) or furosemide (OAT3 substrate) to healthy subjects with elevated oxobutyric acid metabolite (inhibitor of OATP1B1 and OAT3) plasma concentrations did not meaningfully alter the pharmacokinetics of rosuvastatin or furosemide. See also section 4.5.

Elimination

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

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 7.5 mg to 60 mg.
Pharmacokinetics in special patient groups
Age
Clearance of tolvaptan is not significantly affected by age.

Hepatic impairment
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 mg 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 oedema, 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-times and 2.3-times higher than that in healthy subjects.

Renal impairment
In an analysis on population pharmacokinetics for patients with heart failure, tolvaptan concentrations of patients with mildly (creatinine clearance [C_{cr}] 50 mL/min to 80 mL/min) or moderately (C_{cr} 20 mL/min to 50 mL/min) impaired renal function were not significantly different to tolvaptan concentrations in patients with normal renal function (Ccr 80 mL/min 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.

IV.3 Pharmacodynamics

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

In healthy adult subjects, oral administration of 7.5 mg to 120 mg doses of tolvaptan produced an increase in urine excretion rate within 2 hours of dosing. Following single oral doses of 7.5 mg to 60 mg, 24-hour urine volume increased dose dependently with daily volumes ranging from 3 to 9 litres. For all doses, urine excretion rates returned to baseline levels after 24 hours. For single doses 60 mg to 480 mg, 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.

IV.4 Clinical Efficacy

No new clinical efficacy studies were performed.

IV.5 Clinical Safety

No new clinical safety studies were performed. No concerning safety signals were identified during the BE study which was performed.

A risk management plan was submitted, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tolvaptan Ascend 7.5mg tablets.

Safety specification

Important identified risks	• Too rapid rise of serum sodium and neurologic sequelae (encephalopathy, osmotic demyelination) • Interaction with CYP3A4 inhibitors

	• Volume depletion, dehydration and associated sequelae such as renal dysfunction
Important potential risks	• Raised intraocular pressure/glaucoma
Missing information	• Paediatric use • Pregnancy outcome data • Use in breastfeeding • Off-label use • Use in hepatic impaired patients

Routine pharmacovigilance and risk minimisation activities are sufficient to identify, characterise, prevent or minimise risks relating to Tolvaptan Ascend 7.5mg tablets.

Periodic Safety Update Reports (PSURs) shall be submitted 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.

IV.6 Discussion on the clinical aspects

Samsca has been shown to be effective at increasing sodium levels, particularly in patients with SIADH and tolvaptan ascend has performed the necessary studies to demonstrate that it is bioequivalent to this already approved application. This generic application minimises the need for further human studies.

V. OVERALL CONCLUSIONS

Tolvaptan ascent 7.5mg oral tablet is a generic form of Samsca 7.5mg oral tablet. Samsca is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that tolvaptan ascend demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

18.01.2029

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURENUMBER	PRODUCT INFORMATION AFFECTED	DATEOF STARTOF PROCEDURE	DATEOF END OF PROCEDURE
New DCP as RMS	IE/H/1249/001/DC	SPC, IPAR	10th May 2024	9th May 2029