26 January 2023
EMA/369354/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tolvaptan Accord

International non-proprietary name: tolvaptan

Procedure No. EMEA/H/C/005961/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACTIV	Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist
ADH	Antidiuretic Hormone
AE	Adverse Events
Alu	Aluminium
API	Active pharmaceutical ingredient
aPTT	Activated Partial Thromboplastin Time
ASMF	Active Substance Master File
AVP	Arginine Vasopressin
BE	Bioequivalence
BCS	Biopharmaceutics Classification System
cAMP	Cyclic Adenosine Monophosphate
CFU	Colony Forming Units
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human use
CYP3A4	Cytochrome P450 3A4
DMF	Drug master File
EC	European Commission
EF	Ejection Fraction
EIPNA	N-Nitrosoethylisopropylamine
EPAR	European Public Assessment Report
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HF	Heart Failure
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalized Ratio

IR	Infrared
KF	Karl Fischer Titration
LoD	Limit of Detection
LoQ	Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorisation Application
MO	Major Objection
NDEA	N-Nitrosodiethylamine
NDIPA	N-Nitrosodiisopropylamine
NDMA	N-Nitrosodimethylamine
NfG	Note for Guidance
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia
PT	Prothrombin Time
PVC	Polyvinyl chloride
QC	Quality Control
RH	Relative Humidity
RMP	Risk Management Plan
RP	Restricted Part (or Closed Part) of an ASMF
SIADH	The Syndrome of Inappropriate Secretion of Antidiuretic Hormone
SmPC	Summary of Product Characteristics
SLS	Sodium Laurilsulfate
TEAEs	Treatment Emergent Adverse Events
UV	Ultraviolet
V2R	V2 Vasopressin Receptor
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 29 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Tolvaptan Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 June 2021.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> *Tolvaptan is indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Samsca instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Samsca, 7.5 mg, 15 mg, 30 mg, tablet
- Marketing authorisation holder: Otsuka Pharmaceutical Netherlands B.V., Netherlands
- Date of authorisation: 02-08-2009
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/09/539/001-008

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Samsca, 7.5 mg, 15 mg, 30 mg, tablet
- Marketing authorisation holder: Otsuka Pharmaceutical Netherlands B.V., Netherlands
- Date of authorisation: 02-08-2009
- Marketing authorisation granted by:
  - Union

- Union Marketing authorisation number: EU/1/09/539/001-008

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Samsca, 30 mg, tablet
- Marketing authorisation holder: Otsuka Pharmaceutical Netherlands B.V., Netherlands
- Date of authorisation: 03-08-2009
- Marketing authorisation granted by:
  - Union
  - Union Marketing authorisation number(s): EU/1/09/539/003-004
- Bioavailability study number(s): 031-BE-2020

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alar Irs

The application was received by the EMA on	29 November 2021
The procedure started on	24 December 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 March 2022
The PRAC Rapporteur's first Assessment Report was circulated to all	25 March 2022

PRAC and CHMP members on	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 August 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	20 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	05 October 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	21 December 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 January 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tolvaptan Accord on	26 January 2023

2. Scientific discussion

2.1. Introduction

This marketing authorisation application for Tolvaptan Accord, 7.5 mg, 15 mg and 30 mg tablet, is a generic application of a centrally authorised medicinal product according to Art. 10(1) of Directive 2001/83/EC, as amended. In this assessment report, the name Tolvaptan Accord is used. The reference product Samsca, 7.5 mg, 15 mg, 30 mg, tablet, marketed by Otsuka Pharmaceutical Netherlands B.V., Netherlands, was first authorised in the European Union on 03 August 2009 via the centralised procedure (EU/1/09/539). The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Samsca instead of non-clinical and clinical data.

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, resulting in free water diuresis in the treatment of euvolemic or hypervolemic hyponatremia. Tolvaptan affinity for the human V2-receptor is 1.8 times that of native AVP.

Tolvaptan is authorised for the treatment of abnormally low levels of sodium in the blood in adults with a condition called 'syndrome of inappropriate antidiuretic hormone secretion' (SIADH). In SIADH, an excessive amount of the hormone vasopressin makes the patient produce less urine and thereby retain more water in the body, which dilutes the concentration of sodium in the blood. By blocking vasopressin V2-receptor tolvaptan prevents vasopressin's effect increasing urine production, decreasing the amount of water in the blood and increasing the blood sodium level.

Treatment with tolvaptan should be started in hospital so that healthcare professionals can determine the most appropriate dose and monitor the patient's level of blood sodium and blood volume. The starting dose is 15 mg once daily. The dose may be increased to a maximum of 60 mg once a day to achieve an appropriate level of blood sodium and blood volume. A dose of 7.5 mg once a day can be used for patients at risk of excessively quick rise in blood sodium.

Use of tolvaptan in combination with other options may increase the risk of overly rapid correction of serum sodium. For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels must be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatremia, 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 hyponatremia is no longer a clinical issue.

Therapeutic indication

Tolvaptan is indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 7.5 mg, 15 mg, or 30 mg of tolvaptan.

Other ingredients are: Lactose monohydrate, microcrystalline cellulose, magnesium stearate, croscarmellose sodium, hydroxypropyl cellulose, maize starch, and indigo carmine aluminium lake (E132).

The product is available in perforated unit dose PVC/Alu blisters, as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of tolvaptan is (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl)carbonyl]-o-tolu-m-toluidide corresponding to the molecular formula $C_{26}H_{25}ClN_2O_3$. It has a relative molecular mass of 448.94 g/mol and the following structure:

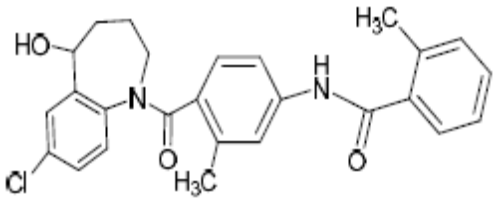

Figure 1: Active substance structure

The chemical structure of tolvaptan was elucidated by a combination of UV, FT-IR, proton NMR, C^{13} NMR, and mass spectroscopic studies. The solid state properties of the active substance were determined by XRD and thermogravimetric analysis.

The active substance is a white to off-white crystalline powder, practically insoluble in water, it is non hygroscopic. The active substance is freely soluble in a mixture of ethanol and methylene chloride (ratio 60:240). The active substance is micronised to achieve a specific particle size distribution. Micronisation is not considered critical to the finished product manufacturing process considering the dissolution that takes place at the beginning of this process.

Tolvaptan exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is routinely controlled by a test for specific optical rotation.

Polymorphism has been investigated for tolvaptan. The applicant has demonstrated via XPRD that the polymorphic form produced is in line with the reference product. It has also been demonstrated that the polymorph manufactured is stable during storage. A regular test for polymorphic form is included in the active substance specification. The polymorphic form of the active substance is not considered to be critical considering the dissolution of the active substance that takes place as part of the finished product manufacturing process.

2.2.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. One manufacturer is proposed for the active substance tolvaptan.

Tolvaptan is synthesised in four main steps using well-defined starting materials with acceptable specifications. The selection of the starting materials was appropriately justified.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. During the procedure sufficient information was provided regarding the control of genotoxic impurities in the starting materials and the intermediates in line with ICH M7.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The manufacturing process development for the active substance was clarified during the procedure. The development is adequate, and the manufacturer has demonstrated the ability to reproducibly produce the active substance to the required standard.

The active substance is packaged in double polyethylene bags (outer black) in triple laminated polyethylene bag, placed in a HDPE container which complies with EC 10/2011 as amended and Ph. Eur. 3.1.3.

2.2.2.3. Specification(s)

The active substance specification includes tests for appearance, identity (IR, HPLC, XPRD, Specific Optical Rotation), assay (HPLC), impurities (HPLC), residual solvents (GC), residue on ignition (Ph. Eur.) particle size (laser light diffraction), loss on drying (Ph. Eur.).

The finished product manufacturer applies the same quality requirements for the active substance as proposed by the active substance production site. The limits of specified and unspecified impurities described in the documentation comply with the relevant ICH guidelines. The limit for total impurities is justified based on the actual batch data and stability results.

The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Satisfactory certificates of analysis of two micronised active substance production batches from the active substance manufacturer and the finished product manufacturer are presented. Additionally, batch analyses results have been provided for 3 recent production batches of micronised tolvaptan in section 3.2.S.4.4 of ASMF applicant’s part. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period.

Stability data from four full scale batches of active substance from the proposed manufacturer stored in the

intended commercial package for up to 72 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested during stability: description, polymorphic form, loss on drying, related substances, and assay. Optical rotation testing will also be included during ongoing stability testing. The analytical methods used were the same as for release and were stability indicating.

All the results remain within the acceptance limits at all conditions tested. There are no clear trends to be observed in the results. The level of related substances changes on stability is very low. No significant differences in other quality parameters have been observed on micronised batch during storage compared to non-micronised batches. It can be concluded that the micronisation process described in the ASMF does not negatively influence the stability of the active substance.

Photostability testing following ICH guideline Q1B was performed on 1 batch. Tolvaptan is sensitive to light, therefore the storage statement "Preserve in well closed-containers" is justified. Results on stress conditions under acid, base, oxidative, thermal conditions, hydrolytic degradation and humidity degradation were also provided. Tolvaptan is stable to heat at 60°C, 75% RH and water hydrolysis at 60°C. In contrast tolvaptan is sensitive to acid, sensitive to basic conditions, and peroxide at 60°C.

The defined expiry date of 60 months established by the ASMF-holder can be accepted based on the available data. No restrictions concerning temperature storage conditions are needed. However, active substance manufacturer has established the following storage conditions: Preserve in well closed-containers at controlled room temperature. As the active substance is only handled by the manufacturing sites and it is not causing any additional burden for patients a request to omit any statements for storage conditions was not outlined. The finished product manufacturer uses shorter re-test period than the active substance manufacturer - 12 months instead of 60 months – while applying the same storage conditions. This is similarly considered acceptable.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is presented as tablets containing 7.5 mg, 15 mg, or 30 mg of tolvaptan as active substance. The visual descriptions of the tablets are as follows:

Strength	**Product Description**
Tolvaptan 7.5 mg tablets	Light blue to blue coloured, round, biconvex, uncoated tablets debossed with "MT" on one side and "18" on other side.
Tolvaptan 15 mg tablets	Light blue to blue coloured, triangle, biconvex, uncoated tablets debossed with "MT" on one side and "7" on other side.
Tolvaptan 30 mg tablets	Light blue to blue coloured, round, biconvex, uncoated tablets debossed with "MT" on one side and "8" on other side.

All compendial excipients are tested according to the corresponding Ph. Eur. monographs and meet the specified requirements. Colouring mixture indigo carmine aluminium lake (E132) is used as a colouring

excipient. The choice of excipients is justified and their functions explained. The product is available in PVC/Aluminium unit dose blisters.

The finished product has been developed to be a generic equivalent to the reference medicinal product Samsca. Consequently, the objective was to prepare a tablet essentially similar to the reference medicinal product. A summary of formulations used during development is provided. Changes between the proposed commercial formulation batches and those batches used in formulation studies were described and the rationale for the changes made has been provided.

Tolvaptan Accord tablets have the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as the reference product. All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Similar composition in terms of excipients is proposed as approved for the reference product. There is no effect of croscarmellose sodium, which is present in the proposed product only, on the performance of the product in comparison to the reference product as bioequivalence (BE) has been demonstrated.

The chosen formulation adequately accommodates the active substance's physicochemical properties i.e. solubility, route of administration. The active substance is classified as a BCS class 4 substance - with low solubility and low permeability across the physiological pH range. In order to improve the dissolution and thereby enhance the bioavailability, amorphous form of the active substance is used in the tablet formulation. The amorphous form is controlled during manufacture by X-ray diffraction. The data provided demonstrate that no amorphous-crystalline conversion occurs during manufacture or storage. Thus, the physical characteristics with the potential impact to the finished product quality such as particle size, crystalline configuration of the neat active substance, do not have any direct impact on the tablet formulations.

Manufacturing process development has been sufficiently discussed in order to have an overview of each phase. Wet granulation (fluid bed) was selected considering the high proportion of active substance in the finished product and the process enables the conversion of the polymorphic state of the drug substance to the amorphous form. This type of manufacturing process is also used for the reference product according to EPAR. Based on the provided information no new technologies are introduced, hence the manufacturing method is satisfactorily justified conventional manufacturing process. The development activities conducted and batches manufactured to date have established acceptable ranges for key process parameters of the manufacturing process at commercial scale, demonstrating the manufacturing process is robust and reproducible.

Bioequivalence (BE) study was performed showing bioequivalence between the 30 mg proposed formulation and the reference product of the same strength. The applicant has performed the required comparative dissolution studies between test product and reference product bio-batches over the physiological pH range with and without surfactant and in the QC media. Although in vitro dissolution similarity between the bio-batch and the reference product was not confirmed in all media (by $\geqslant$85% dissolution in 15 min or by mathematical evaluation in case of incomplete release), the results of the successful in vivo bioequivalence study prevail.

In addition, a request for biowaiver of additional strengths i.e. 7.5 mg and 15 mg was requested according to the general biowaiver requirements. The in vitro dissolution tests comparing the in vitro dissolution similarity between biowaiver strengths and the bio-batch strength over physiological pH range with and without surfactant and in QC media were conducted. Moreover, comparisons at the same dose (4 x 7.5 mg tablets vs 1 x 30 mg tablet or 2 x 15 mg tablets vs 1 x 30 mg tablet) were performed to justify that differences in

dissolution between strengths are active substance rather than finished product related.

The biowaiver for additional strengths is justified, since tolvaptan tablets comply with general requirements i.e. linear pharmacokinetics, same manufacturer and manufacturing process, same qualitative composition, the composition quantitatively proportional. In all media with surfactant SLS, similarity of dissolution between the bio-batch strength and biowaiver strengths was demonstrated as more than 85% of tolvaptan was dissolved within 15 minutes. In media without surfactant, drug release was incomplete and dissolution profiles were concluded to be similar as calculated f2 similarity values were $\geqslant$ 50, either in 1 tablet vs 1 tablet or in same dose comparison.

The development of the test conditions of the QC dissolution method has been discussed. Influence of different media and stirring speeds on dissolution has been evaluated. All batches used in the clinical studies were tested at release and during stability using the QC method. The applicant has demonstrated that the current method has sufficient discriminatory ability to reliably detect the physical state of tolvaptan drug substance.

The primary packaging is perforated unit dose PVC/Alu blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of eight main steps: sifting of raw materials, preparation of drug solution, spraying and wet granulation followed by drying, sifting and mixing of dried granules, pre-lubrication, lubrication, compression and packaging. The description of manufacturing process is in line with manufacturing process development. The process is considered to be a standard manufacturing process.

The proposed commercial batch size is acceptable. The tablets are manufactured from common blend. This approach is acceptable.

Information about the equipment used, the applied process parameters including sieve sizes and mixing times is outlined in the manufacturing process narrative and is in line with process validation.

Process control of critical steps (drying, blending, compression and packaging) were provided together with test methods and acceptance criteria and are considered acceptable to reduce the risks identified during formulation and process development. The in-process controls are in general adequate for this type of manufacturing process and pharmaceutical form.

The applicant has defined bulk holding times that are supported with sufficient stability data.

Major steps of the manufacturing process have been validated by a number of studies on three production scale batches of common blend, further divided for different strengths. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specification(s)

The finished product release specifications include appropriate tests for this kind of dosage form including; appearance, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), content uniformity (Ph. Eur.), dissolution (in-house), microbiological quality (Ph. Eur.), water content (KF).

Tests and limits for degradation products have been justified in line with current regulatory guidance and batch data.

The specification limit for dissolution is based on the dissolution results of bio-batch, it can be considered acceptable in accordance with the "reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action" (EMA/CHMP/CVMP/QWP/336031/2017).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

The risk evaluation concerning the presence of nitrosamine impurities in the finished product has been updated (as requested to address a MO) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). As a precautionary measure, the drug product manufacturer has analysed three production scale batches for the presence of nitrosamine impurities (NDMA, NDEA, EIPNA, NDIPA) in drug product. In support of the omission of testing nitrosamines NDMA, NDEA, EIPNA, NDIPA in the drug product it has been demonstrated using the adequately sensitive and specific analytical method that the respective single nitrosamines are consistently at or below 10 % of the acceptable intake. The data presented can be considered sufficient to confirm that potential risk for nitrosamine formation in particular medicinal products is remote and further testing in the final drug product is not needed.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 2 batches of the drug product per strength (6 total) batches at commercial scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from two commercial scale batches per strength of finished product stored for up to 18 months under long term conditions (i.e. 25ºC / 60% RH) and for up to 6 months under accelerated conditions (i.e. 40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of tolvaptan tablets medicinal product are identical to those proposed for marketing and were packed in the primary packaging (blister packs) as for marketing. As the submission includes data from stability studies on fewer than three production scale batches per each strength, a commitment has been made in section 3.2.P.8.2 to continue the long term studies through the proposed shelf life, and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

Samples were tested for appearance, assay by HPLC, related substances by HPLC, dissolution by UV, water by KF and microbiological quality. All results remained within the acceptance criteria for all quality attributes tested with no significant changes. The stability batches were all of a consistent quality.

Photostability was carried out on three different sets of samples (Open exposure sample, Packed sample and Dark control) same sample exposed to both the cool white fluorescent and near ultraviolet lamp two different light exposure conditions as per ICH Q1B Option-2 on 7.5 mg and 30 mg Tolvaptan tablets. The product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 24 months and with no special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.2.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products.

No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Earlier raised major objections related to mutagenic impurities, the nitrosamines risk assessment, and GMP compliance of a site proposed for secondary packaging. These objections were satisfactorily resolved during the procedure. A sufficient assessment of potential mutagenic impurities in the active substance was provided in line with ICH M7. The nitrosamine risk assessment was updated to account for all current risk factors described in the Q&A on nitrosamines (EMA/409815/2020). Testing data was also provided for some small nitrosamine molecules and demonstrated that these nitrosamines were not of concern. The issue related to GMP compliance was resolved by removing the proposed activity for which an inspection had not been conducted from the application. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

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.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) studies were submitted. This was justified by the applicant as the introduction of Tolvaptan Accord marketed by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all tolvaptan containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview is based on published literature data. This is acceptable since tolvaptan is a well-known active substance and essential similarity is claimed to the reference product. The non-clinical section in the SmPC is identical to the reference product.

The justification for the lack of full Environmental Risk Assessment was further substantiated during the procedure to support the claim that an increase in environmental exposure of the active substance is not to be expected.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Tolvaptan Accord and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for tablets containing tolvaptan. To support the marketing authorisation application the applicant conducted a bioequivalence study with a cross-over design under fasting conditions. This study was the pivotal study for the application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of tolvaptan based on published literature. The SmPC is in line with the SmPC of the reference product.

GCP aspect

The clinical trials were performed in accordance with GCP as claimed by the applicant.

Exemption

A bioequivalence study has been performed on tolvaptan 30 mg tablets. In addition, a request for waiver of bio-study for additional strengths i.e. 7.5 mg and 15 mg is being placed according to the general biowaiver requirements (Ref: Guideline on the Investigation of Bioequivalence, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/Corr**):

a) All the strengths *i.e*. 7.5 mg, 15 mg and 30 mg of proposed pharmaceutical product are manufactured by the same manufacturer using the same manufacturing process;

b) The qualitative composition of the different tolvaptan tablet strengths is the same;

c) The compositions of the strengths are quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance(s) is the same for all strengths;

d) The dissolution profiles are similar under identical conditions for the additional strengths compared to the batch used in the bioequivalence study.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 031-BE-2020: An open label, balanced, randomized, two-treatment, two-period, two-sequence, two-way cross-over, single oral dose, bioequivalence study of Tolvaptan Tablets 30 mg of MSN Laboratories Pvt Limited, India comparing with Samsca 30 mg tablets of Otsuka Pharmaceutical Netherlands B.V., Netherlands in healthy, adult, human, subjects under fasting conditions.

Methods

Study no. 031-BE-2020 was an open-label, analyst-blinded, balanced, randomised, two-period, two-sequence, two-way cross-over, single dose bioequivalence study in healthy adult subjects under fasting conditions with a wash out period of 4 days between two administrations. In each period single dose of either test or reference product of 30 mg tolvaptan tablets was administered orally according to the randomisation scheme.

Food and fluid intake

Subjects were confined to the clinical facility at least 11 hours prior to drug administration and remained at the study centre until their 48 hrs post-dose in period 2. After an overnight fast of 11 hours, subjects were administered a single 30 mg dose as a tablet of either the test or the reference product in sitting posture with 240 ± 2 mL of drinking water. The standardised meals were provided to subjects at 4-, 8- and 13-hours post-dose on the first day and on appropriate times from thereafter during their stay in the clinical facility. The meal plan was kept identical in both the study periods. Subjects were instructed to drink water or other fluids at the first sign of thirst in order to avoid excessive thirst or dehydration.

Sampling schedule

22 blood samples (1 x 4 mL) were collected per subject in each period for the assessment of tolvaptan in plasma. Blood collections were performed prior to the administration of study medication (0; pre-dose within a period of 90 minutes before dosing) and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00- and 48.00-hours following study drug administration. The washout period of 4 days was kept between two consecutive dosing periods. Total blood loss for a subject during the entire study did not exceed 228 mL.

Test and reference products

Test Product: Tolvaptan tablets 30 mg manufactured by MSN Laboratories Private Limited, India.

Reference Product: Samsca 30 mg tablets marketed by Otsuka Pharmaceutical Netherlands B.V., Netherlands.

Population(s) studied

A total of 38+2 additional stand-by healthy subjects were enrolled in the study. 38 subjects (Asian race, male, aged 19-42 years, BMI 19.03 – 29.84 kg/m^2) completed both study phases and were included in the pharmacokinetic and statistical analysis. Only non-smokers were allowed in this study.

Drop-outs: There were no drop-outs in the study.

None of the subjects used any concomitant medication for at least two weeks prior to check-in until the study completed.

Analytical methods

An analytical LC-MS/MS method for the estimation of tolvaptan concentrations in human K_2EDTA plasma was developed and validated at the analytical study site. Tolvaptan-D7 was used as an internal standard.

Blood samples were collected into K_2EDTA vacutainers and centrifuged 4000 rpm for 10 minutes at 4°C ± 2°C. The plasma samples were frozen and retained at -70°C ± 10 °C until assay. Study drug was extracted from 200 µl of liquid-liquid extraction method. From instrumentation LC-MS/MS from AB Sciex (models API-4000 and API-4500) and Analyst software Version 1.7.2 for data processing were used.

Method validation

The LS-MS/MS method was validated over a concentration range of 3.079 ng/mL to 1796.515 ng/mL of tolvaptan with LLOQ 3.079 ng/mL. The calibration standard curve was composed of 10 non-zero levels: 3.079, 6.158, 18.604, 57.776, 144.440, 361.099, 722.199, 1077.909, 1437.212 and 1796.515 ng/mL of tolvaptan. The QC sample concentrations at LLOQ QC 3.089 ng/mL, LQC 8.752 ng/mL, MQC1 190.261 ng/mL, MQC2 694.382 ng/mL, HQC 1388.764 and DIQC (1:3) 5786.518 ng/mL were used throughout the validation. The mean overall recovery from plasma was 100.24% for tolvaptan and 102.49% for tolvaptan-D7.

Method performance characteristics were following:

Within-run precision (%CV)	1.41% - 3.42%	LLOQ QC: 1.59% - 4.00%
Within-run accuracy	102.32% - 111.45%	LLOQ QC: 96.81 – 103.94%
Between-run precision (%CV)	1.75% - 3.05%	LLOQ QC: 4.06%
Between-run accuracy	103.02% - 110.70%	LLOQ QC: 99.86%
Dilution integrity accuracy 1:3 dilution	0.75%	
Dilution integrity precision 1:3 dilution (%CV)	93.45%	

The linear calibration curve calculated by weighted linear regression (weight = $1/x^2$) was used for calculation of sample concentration.

Pre-study validation and bio-analytical report were provided. The method selectivity and sensitivity were demonstrated. Stability of analytes at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation. Dilution integrity, carryover and matrix effect were tested.

One method validation addendum was included in the documentation – Addendum-I (dated Aug 04, 2021) covering results of selectivity, long-term stability at -70±10°C for 155 days 13 hrs, carry-over test and accuracy & precision batch.

Study sample analysis

A total of 1672 study samples were received and analysed in 24 analytical runs out of which 21 analytical runs were valid.

Calibration curve standards:
Calibration curve ranged from 3.079 to 1791.336 ng/ml of tolvaptan. Accuracy and precision were 97.34% to 102.98% and 1.10 to 3.64%, respectively. Correlation coefficients (r) were equal to or greater than 0.9962 in analytical runs. Number of successful calibration curves used with the study samples was 21.

QC samples:
The quality control (QC) concentrations were 8.738 (LQC), 189.962 (MQC1), 693.294 (MQC2), 1386.587 (HQC) ng/mL for study sample analysis. Between-run precision and accuracy were 0.39 to 9.61% and 94.67 to 107.50%, respectively. 6 QC samples were outside of the acceptance range.

Reanalysis of study samples: In total 406 samples (24.3% of 1672 samples) were re-assayed. This included:

- re-analysis of 3 full batches; 1 batch was re-analysed due to ISTD variation and 2 batches as calibration standards & QC samples did not meet the acceptance criteria.
- re-analysis of all the samples for two subjects due to ISTD variation;
- re-analysis of 10 individual samples out of which 4 were analysed for analytical reasons (ISTD variation, unacceptable chromatography) and 6 in error. For samples re-analyzed in error, initial values were reported.

No batches nor individual samples were re-integrated.

Incurred sample reanalysis: conducted on 152 samples (9.1 % of 1672 samples). 99.34% (151/152) of concentrations obtained by reanalysis were found within 20% of their mean initial value.

Long-term stability of samples: The maximum study sample storage period from first blood draw (Jul 20, 2021) to last sample analysis (Aug 10, 2021) was 22 days. The long-term stability data of tolvaptan in human plasma covers 155 days 13 hrs at -70±10^{o}C (Addendum I).

All concentration values below limit of quantification were reported as BLQ and set as zero for PK analysis. The same equipment was used analysis of samples and precision and accuracy validation. The number of QC samples was adequate, i.e. at least two QC sets or at least 5% of the total number of subject samples.

Pharmacokinetic Variables

Primary pharmacokinetic parameters: C_{max} and AUC_{0-t}

Secondary pharmacokinetic parameters: T_{max}, K_{el}, $T_{1/2}$, $AUC_{0-\infty}$, $AUC_{\%extrapolation}$

Statistical methods

The pharmacokinetic parameters for tolvaptan were calculated from the plasma concentration vs. time profile using Phoenix WinNonlin Version 8.3. Statistical analysis was carried out using SAS software version 9.4 for Windows.

PK parameters for each individual were tabulated and graphically presented. Actual time-points of the sample collection were used for the calculation of PK parameters. All concentration values below the lower limit of quantification were set to zero for all pharmacokinetic and statistical calculations.

The arithmetic mean, minimum, maximum, median, standard deviations and the coefficient of variation was reported for the pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, K_{el} and $AUC_{\% \text{ extrapolation}}$) of untransformed data. The geometric means and the coefficient of variation were reported for C_{max} and AUC_{0-t} of log-transformed data. Linear trapezoidal method was used in the study.

The log-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} were analyzed using GLM ANOVA Model (PROC GLM) of SAS® software. ANOVA model included Sequence, Subject (Sequence), Period and Treatment as fixed effects. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5 % (alpha=0.05).

90% confidence intervals for the ratios of test and reference product averages were calculated using the ANOVA output from the analysis of the log-transformed data. Consistent with the two one sided test for bioequivalence, the 90% confidence interval for the ratio of both the products averages (geometric means) was calculated by first calculating the 90% confidence interval for the differences in the averages (arithmetic means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.

No protocol deviations were reported.

Criteria for conclusion of bioequivalence:

Bioequivalence of the test product that of the reference product will be concluded as comparable if the 90% confidence interval falls within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameter C_{max} and AUC_{0-t} for tolvaptan.

Results

Table 1: Pharmacokinetic parameters for tolvaptan (non-transformed values)

Pharmacokinetic parameter	Test N=38		Reference N=38	
	arithmetic mean **geometric mean**	**SD** **CV%**	**arithmetic mean** **geometric mean**	**SD** **CV%**
$AUC_{(0-t)}$ (ng*h/mL)	**3463.2245** 3217.2671	± 1274.90437 36.81%	**3436.2663** 3206.0014	± 1275.30667 37.11%
$AUC_{(0-\infty)}$ (ng*h/mL)	3555.8279 3300.7433	± 1334.60695 37.53%	3534.2499 3286.6107	± 1360.78496 38.50%
C_{max} (ng/mL)	**401.2865** 381.9198	± 121.85089 30.37%	**385.7057** 366.9175	± 122.00855 31.63%
T_{max}* (h)	2.00	0.67 - 5.00	2.51	1.00 – 5.00

AUC_{0-t}	area under the plasma concentration-time curve from time zero to last measurable concentration
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

Table 2: Statistical analysis for tolvaptan (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
$AUC_{(0-t)}$	**100.35**	95.77 – 105.15	12.11
C_{max}	**104.09**	96.34 – 112.46	20.17

* estimated from the Residual Mean Squares

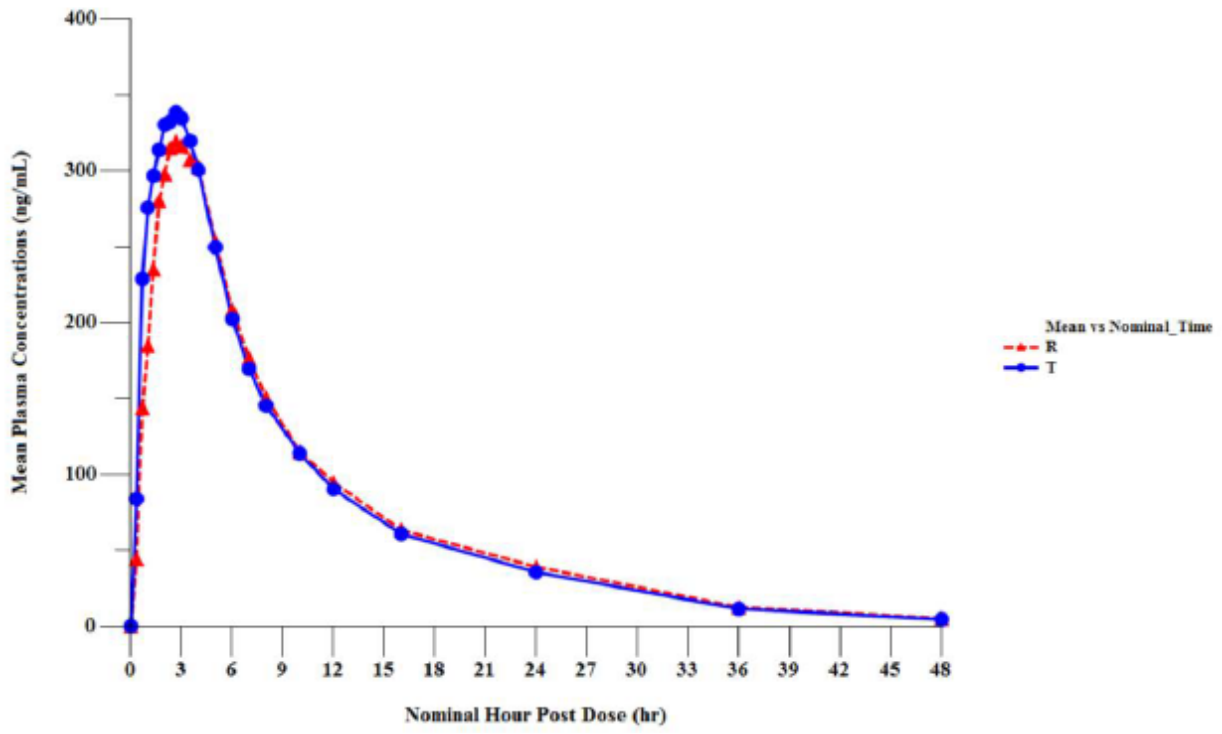

Figure 2: Mean plasma concentration vs. time curve for tolvaptan after administration of test and reference formulations (30 mg) to healthy subjects (N=38).

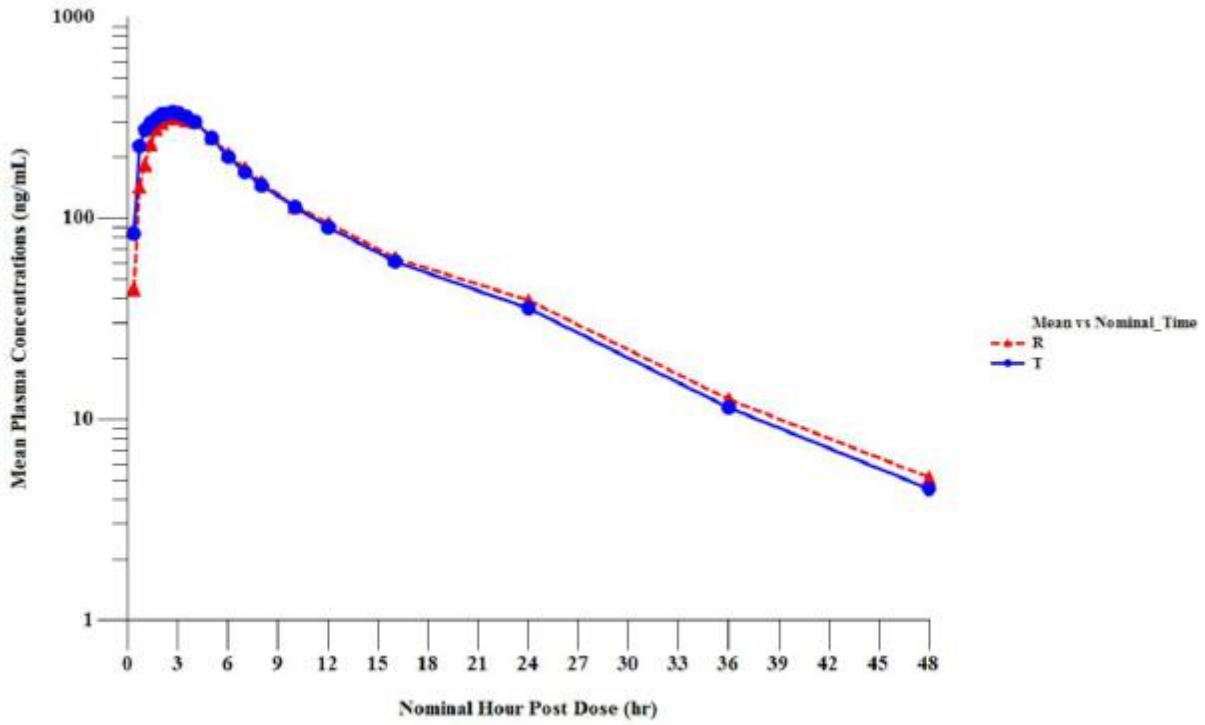

Figure 3: Semi-logarithmic plot of mean plasma concentration vs. time curve for tolvaptan after administration of test and reference formulations (30 mg) to healthy subjects (N=38).

Based on the ANOVA results, no significant sequence, period and formulation effects were observed for log-transformed pharmacokinetic parameters C_{max} and AUC_{0-t}.

Safety data

A total of 5 adverse events (AEs) were reported in 4 subjects during this study.

There were no AEs reported during in-house study periods.

All AEs reported during post-study assessment. Increased lymphocytes were reported in 2 subjects, increased eosinophils in 1 subject, increased AST in 1 subject and increased ALT in 1 subject.

All AEs were mild in severity and were considered as resolved except for 2 subjects who were lost to follow up. No serious AEs and deaths were reported during the entire study.

Pharmacokinetic conclusion

Based on the presented bioequivalence study, Tolvaptan 30 mg tablets manufactured by MSN Laboratories Private Limited, India are considered bioequivalent with Samsca 30 mg tablets marketed by Otsuka Pharmaceutical Netherlands B.V., Netherlands.

The results of study no. 031-BE-2020 with 30 mg formulation can be extrapolated to other strengths 7.5 and 15 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2.3. Additional data

The applicant has performed the required comparative dissolution studies between test product and reference product bio-batches over the physiological pH range with and without surfactant and in QC media. Although *in vitro* bioequivalence based on similar dissolution between bio-batches was not confirmed in all media (by ≥85% dissolution in 15 min or by mathematical evaluation in case of incomplete release), the results of the successful *in vivo* bioequivalence study prevail.

2.4.2.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical pharmacology

To support the application, the applicant has submitted a single dose cross-over bioequivalence study under fasting conditions to demonstrate essential similarity with the reference product Samsca 30 mg tablets marketed by Otsuka Pharmaceutical Netherlands B.V., Netherlands. According to the SmPC of the reference product, the pharmacokinetics of tolvaptan appears linear over the therapeutic dosage range and tolvaptan can be taken without regard to meals. Therefore, the selection of the highest dose, 30 mg, to be used in the bioequivalence study under fasting conditions is justified and in accordance to guidelines.

The overall study design is acceptable and in line with the pharmacokinetic properties of tolvaptan. The bioequivalence study was conducted under standardised conditions; however, water consumption was not restricted as treatment with tolvaptan may result in severe dehydration. The sampling time schedule and wash-out period were adequate taking into account the t_{max} and elimination half-life of tolvaptan. The duration of sampling for 48 hours was sufficient as the residual areas were found to be lower than 20% for all subjects and treatments.

Data regarding the test and reference product was sufficient.

The population was chosen according to the guidelines. Bioanalytical method had satisfactory performance and was adequately validated. The pharmacokinetic and statistical methods applied were appropriate for a single dose study. The 90% confidence intervals for ln-transformed pharmacokinetic variables C_{max} and AUC_{0-t} were within the conventional bioequivalence range of 80.00% to 125.00%.

The pharmacokinetic variables for tolvaptan were comparable between test and reference product. Both formulations were well tolerated in the study.

Additionally, the applicant has requested biowaiver for additional 7.5 mg and 15 mg dosage strengths. To support the request, a justification and results of comparative dissolution tests have been provided. The *in vitro* dissolution tests comparing the *in vitro* dissolution similarity between biowaiver strengths and the bio-batch strength over physiological pH range with and without surfactant and in QC media were conducted. Moreover, comparisons at the same dose (4 x 7.5 mg tablets vs 1 x 30 mg tablet or 2 x 15 mg tablets vs 1 x 30 mg tablet) were performed to justify that differences in dissolution between strengths are drug substance rather than drug product related.

The biowaiver for additional strengths is justified, since tolvaptan tablets comply with general requirements *i.e.* linear pharmacokinetics, same manufacturer and manufacturing process, same qualitative composition, composition quantitatively proportional. In all media with surfactant SLS, similarity of dissolution between the bio-batch strength and biowaiver strengths was demonstrated as more than 85% of tolvaptan was dissolved within 15 minutes. In media without surfactant, drug release was incomplete and dissolution profiles were concluded to be similar as calculated f2 similarity values were ≥ 50, either in 1 tablet vs 1 tablet or in same dose comparison.

Thus, all criteria for a biowaiver according to the Guideline on the Investigation of Bioequivalence are fulfilled.

2.4.4. Conclusions on clinical pharmacology

Based on the presented bioequivalence study, Tolvaptan 30 mg tablets manufactured by MSN Laboratories Private Limited, India are considered bioequivalent with Samsca 30 mg tablets marketed by Otsuka Pharmaceutical Netherlands B.V., Netherlands.

The results of study no. 031-BE-2020 with the 30 mg formulation can be extrapolated to the other strengths 7.5 and 15 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.

The application is approvable from the clinical perspective.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 13: Summary of safety concerns

Important identified risks	• Volume depletion, dehydration and associated sequelae such as renal dysfunction
Important potential risks	• None
Missing Information	• Pregnancy outcome data • Off-label use • Use in hepatic impaired patients

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of tolvaptan tablets. The reference product Samsca is indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and is considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these aspects was based on information from published literature and is considered sufficient.

The bioequivalence study forms the pivotal basis with a single dose cross-over bioequivalence study under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective EU requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Tolvaptan Accord met the protocol-defined criteria for bioequivalence when compared with the reference product Samsca. The point estimates and their 90% confidence intervals for the parameters $AUC_{0-t,}$ AUC_{0-72h}, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated. All criteria for a biowaiver for the additional strengths are fulfilled.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tolvaptan Accord is favourable in the following indication:

Tolvaptan is indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.