Medicines & Healthcare products
Regulatory Agency

# Public Assessment Report

# National Procedure

# Tolvaptan Zentiva 7.5 mg tablets
# Tolvaptan Zentiva 15 mg tablets
# Tolvaptan Zentiva 30 mg tablets
# tolvaptan

## PL 17780/1241-1243

## Zentiva Pharma UK Limited

# LAY SUMMARY

**Tolvaptan Zentiva 7.5mg tablets**
**Tolvaptan Zentiva 15mg tablets**
**Tolvaptan Zentiva 30mg tablets**
**tolvaptan**

This is a summary of the Public Assessment Report (PAR) for Tolvaptan Zentiva 7.5 mg, 15 mg and 30 mg tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Tolvaptan Zentiva in this lay summary for ease of reading.

For practical information about using Tolvaptan Zentiva, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

**What are Tolvaptan Zentiva and what are they used for?**
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Samsca 7.5 mg, 15 mg and 30 mg tablets.

Tolvaptan Zentiva is used to treat low serum sodium levels in adults. The patient has been prescribed this medicine because the patient has a lowered sodium level in the blood as a result of a disease called "syndrome of inappropriate antidiuretic hormone secretion" (SIADH) where the kidneys retain too much water. This disease causes an inappropriate production of the hormone vasopressin which has caused the sodium levels in the blood to get too low (hyponatremia).That can lead to difficulties in concentration and memory, or in keeping one's balance.

**How do Tolvaptan Zentiva work?**
These medicines contain the active substance tolvaptan, which belongs to a group of medicines called vasopressin antagonists. Vasopressin is a hormone that helps prevent the loss of water from the body by reducing urine output. Antagonist means that it prevents vasopressin having its effect on water retention. This leads to a reduction in the amount of water in the body by increasing urine production and as a result it increases the level or concentration of sodium in the blood.

**How are Tolvaptan Zentiva used?**
The pharmaceutical form of these medicines is a tablet and the route of administration is oral (taken by mouth).

Treatment with Tolvaptan Zentiva will be initiated in hospital.

- For treatment of low sodium (hyponatremia), the patient's doctor will start with a dose of 15 mg and may then increase it to a maximum of 60 mg to achieve the desired level of serum sodium. To monitor the effects of Tolvaptan Zentiva the patient's doctor will do regular blood tests. To achieve the desired level of serum sodium the patient's doctor can give in some instances a lower dose of 7.5 mg.
- The patient should swallow the tablet without chewing, with a glass of water.

- The patient should take the tablets once a day preferably in the morning with or without food.

For further information on how Tolvaptan Zentiva are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

**What benefits of Tolvaptan Zentiva have been shown in studies?**
As these Tolvaptan Zentiva medicinal products are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Tolvaptan Zentiva?**
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicines. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

As these Tolvaptan Zentiva medicinal products are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

**Why were Tolvaptan Zentiva approved?**
It was concluded that, Tolvaptan Zentiva have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Tolvaptan Zentiva?**
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Tolvaptan Zentiva. The RMP details the important risks of Tolvaptan Zentiva , how these risks can be minimised, any uncertainties about Tolvaptan Zentiva (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Tolvaptan Zentiva:

| Summary of safety concerns | |
|---|---|
| Important identified risks | Liver Injury in ADPKD patients *(only applicable for ADPKD indication)*<br>Volume depletion, dehydration and associated sequelae such as renal dysfunction |
| Important potential risks | None |
| Missing information | Pregnancy outcome data<br>Off-label use<br>Use in hepatic impaired patients<br>Use in ADPKD patients over the age of 55 years *(only applicable for ADPKD indication)*<br>Long term use of Tolvaptan Tablets in routine medical practice *(only applicable for ADPKD indication)* |

The information included in the SmPCs and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Tolvaptan Zentiva are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

**Other information about Tolvaptan Zentiva**
Marketing Authorisations for Tolvaptan Zentiva were granted in the United Kingdom (UK)d (NI) on 13 March 2025.

The full PAR for Tolvaptan Zentiva follows this summary.

This summary was last updated in May 2025.

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# I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Tolvaptan Zentiva 7.5 mg, 15 mg and 30 mg tablets (PL 17780/1241-1243) could be approved.

The products are approved for the following indication:

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

These medicines contain the active substance tolvaptan. 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.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Samsca 7.5 mg, 15mg and 30 mg tablets that have been licensed for suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence studies were conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 29 August 2024 of because major objections were raised with respect to quality aspects of the dossier. The Committee provisionally concluded that further information on quality aspects should be requested before the product could be approved. In response to the CHM advice, the applicant provided additional data, to address the points that had been raised. Following consideration of the data that were submitted, the approval of the marketing authorisation were recommended.

Marketing Authorisations for Tolvaptan Zentiva were granted in the United Kingdom (UK) on 13 March 2025.

# II QUALITY ASPECTS

## II.1 Introduction

These products contain 7.5 mg, 15 mg or 30 mg of tolvaptan in each tablet.

In addition to tolvaptan, these products also contain the excipients lactose monohydrate, cellulose microcrystalline, povidone, croscarmellose sodium and magnesium stearate

The finished products are packaged in aluminium/polyvinylchloride/aluminium/oriented polyamide (Alu/PVC/Alu/OPA) perforated unit dose blisters, in pack sizes of 1 x 10 tablets

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

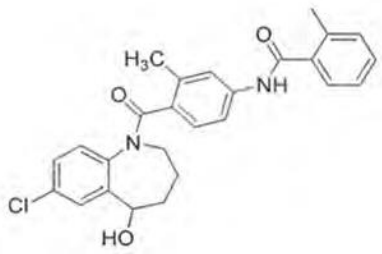
## II.2 ACTIVE SUBSTANCE

**rINN: Tolvaptan**

Chemical Name: 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino) benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine

Molecular Formula: $C_{26}H_{25}ClN_2O_3$

Chemical Structure:




Molecular Weight: 448.94 g/mole

Appearance: White to off white colour powder

Solubility: Freely soluble in N, N-Dimethylformamide, sparingly soluble in benzyl alcohol and methanol and practically insoluble in water

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting suitable retest period when stored in the proposed packaging.

## II.3 DRUG PRODUCTS

### Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with their respective European/national monographs. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

### Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

### Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

### Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions ‘Store in the original package in order to protect from light.’ for the 7.5 mg strength, and without any special storage condition for the 15 mg and 30 mg strengths, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

### II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations was recommended.

## III NON-CLINICAL ASPECTS

### III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of tolvaptan are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

### III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

### III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

### III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

### III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

### III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisations were recommended.

## IV CLINICAL ASPECTS

### IV.1 Introduction
The clinical pharmacology, efficacy and safety of tolvaptan are well-known. With the exception of data from three bioequivalence studies, no new clinical data are provided or are required for applications of this type. An overview based on a literature review and a review of these studies is, thus, satisfactory.

### IV. 2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence studies.

- A pivotal bioequivalence study was submitted in which the pharmacokinetic profile of the 7.5 mg test product was compared with the pharmacokinetic profile of the 7.5 mg strength reference product (Samsca) under fasting conditions.
- Furthermore, applying a bracketing approach and to support a biowaiver of the 15 mg and 30 mg strengths, the applicant submitted comparing a 90 mg strength test product with a 90 mg strength reference product of tolvaptan (Jinarc) under both fasting and fed conditions under both fasting and fed conditions.

**Bioequivalence study 1 (Single dose (7.5 mg), fasting)**
This study was an open label, randomised, single-dose, two-treatment, two-sequence, two-period, crossover oral pivotal bioequivalence study comparing the test product Tolvaptan tablets 7.5 mg versus the reference product Samsca 7.5 mg tablets in healthy, adult, human subjects under fasting conditions.

After a 10-hour overnight fast, subjects were administered a single dose (1 tablet; 7.5 mg) of either the test or reference product with 240 ml of water. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of 11 days between the treatment periods. The plasma concentration of tolvaptan was determined.

A summary of the pharmacokinetic results is presented below:

**Table 1: Bioequivalence results for Tolvaptan 7.5 mg**

| PK Parameters (Unit) | Geometric Least Square Means and its Ratio (N = 47) | | | Intra subject %CV | 90% Confidence Interval | Power (%) |
|---|---|---|---|---|---|---|
| | Test Product (T) | Reference Product (R) | (T/R) (%) | | | |
| $C_{max}$ (ng/mL) | 122.754 | 128.393 | 95.61 | 24.23 | 88.00% - 103.87% | 99.66 |
| $AUC_{0-t}$ (hr*ng/mL) | 790.466 | 845.355 | 93.51 | 22.92 | 86.44% - 101.15% | 99.83 |

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test and reference products under fasting conditions.

**Bioequivalence study 2 (Single dose (90 mg), fasting)**
An open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover oral pivotal bioequivalence study was performed to compare the test product Tolvaptan tablets 90 mg versus the reference product Jinarc 90 mg tablets in healthy, adult, human subjects under fasting conditions**.**

After a 10-hour overnight fast, subjects were administered a single dose (1 tablet; 90 mg) of either the test or reference product with 240 ml of water. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of seven days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

**Table 2: Bioequivalence results for Tolvaptan 90 mg**

| PK Parameters (Units) | Geometric Least Square Means and its Ratio (N = 33) | | | Intra subject %CV | 90% Confidence Interval | Power (%) |
|---|---|---|---|---|---|---|
| | Test Product (T) | Reference Product (R) | (T/R) (%) | | | |
| $C_{max}$ (ng/mL) | 801.472 | 751.678 | 106.62 | 21.84 | 97.40% - 116.72% | 99.07 |
| $AUC_{0-t}$ (hr*ng/mL) | 7610.029 | 7577.566 | 100.43 | 15.70 | 94.07% - 107.22% | 99.99 |

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the 90 mg strength test and reference products under fasting conditions.

As the reference product, used in the bioequivalence study is considered identical to the corresponding strength reference product in the UK (Samsca 90 mg tablets) bioequivalence has also been shown between the proposed product and its UK reference product under fasting conditions.

**Bioequivalence study 3 (single dose (90 mg), fed conditions)**
This study was an open-label, randomised, single-dose, two-treatment, two-sequence, two-period, two-way crossover bioequivalence study comparing the reference product Tolvaptan tablets 90 mg versus the reference product Jinarc 90 mg tablets in healthy, adult human subjects under fed conditions.

After a 10-hour overnight fast, subjects were administered a single dose (90 mg; 1 tablet) of either the test or reference product with 240 ml of water under fed conditions (30 minutes after the intake of a standard high-fat high-calorie breakfast). Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of seven days between the treatment periods.

**Table 3: Statistical results for primary pharmacokinetic parameters**

| PK Parameters (Unit) | Geometric Least Square Means and Its Ratio (N = 65) | | | Intra subject %CV | 90% Confidence Interval | Power (%) |
|---|---|---|---|---|---|---|
| | Test Product (T) | Reference Product (R) | (T/R) (%) | | | |
| $C_{max}$ (ng/mL) | 1181.042 | 1102.899 | 107.09 | 21.89 | 100.50% - 114.10% | 100.00 |
| $AUC_{0-t}$ (hr*ng/mL) | 8452.289 | 8355.148 | 101.16 | 23.89 | 94.41% - 108.39% | 99.98 |

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the 90 mg strength test and reference products under fed conditions.

As the reference product used in the bioequivalence study is considered identical to the corresponding strength reference product in the UK (Samsca 90 mg tablets), bioequivalence has also been shown between the proposed product and its UK reference product under fed conditions.

**Overall conclusion**
As the 15 mg and 30 mg strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence studies on the 90 mg product strength can be extrapolated to the 15 mg and 30 mg strengths, under fasting and fed conditions.

Bioequivalence was also demonstrated under fasting conditions for the 7.5 mg strength; a waiver of the fed study for the 7.5 mg strength can be considered justified.

## IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for these applications and none were required.

## IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

## IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence studies, no new safety data were submitted with these applications.

The safety data from the bioequivalence studies showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence studies.

### IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

### IV.7 Discussion on the clinical aspects

The grant of marketing authorisations were recommended for these applications.

## V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the applications in accordance with legal requirements, including user consultation.

## VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tolvaptan is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The SmPCs, PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisations are recorded in the current SmPCs and/or PIL available on the MHRA website.

| **Application type** | **Scope** | **Product information affected** | **Date of grant** | **Outcome** | **Assessment report attached Y/N** |
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