*CMDh/223/2005*

*February 2014*

**Public Assessment Report**

**Scientific discussion**

**Sonirem, 5 mg and 10 mg Orodispersible tablets**

**Italfarmaco S.p.A.**

**IT/H/0187/002- 003/DC**

**Date: 09/02/2023**

**This module reflects the scientific discussion for the approval of Sonirem, 5 mg and 10 mg Orodispersible tablets. The procedure was finalised at 19/04/2022. For information on changes after this date please refer to the module ‘Update’.**

# INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sonirem, 5 mg and 10 mg Orodispersible tablets, from Italfarmaco S.p.a.

The product is indicated for:

* short-term treatment of insomnia in adults. Benzodiazepines or benzodiazepine-like agents are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

A comprehensive description of the indications and posology is given in the SmPC.

These applications were submitted as:

* a hybrid application under article 10(3) of Directive 2001/83/EC for the 5mg strength;
* a generic application under article 10(1) of Directive 2001/83/EC for the 10 mg strength.

These applications concerned the addition of a new pharmaceutical form (orodispersible tablets - 5 mg and 10 mg strengths) as a line extension of Sonirem, Oral drops solution, which was authorised on 04/29/2010 (DCP number: IT/H/0187/001/DC). This application referred to the reference product Stilnox®, marketed in Italy by Sanofi-Aventis, France, since 05 December 1989.

The reference product for Sonirem Orodispersible tablets was Stilnoct, marketed in UK by Sanofi-Aventis, France, and registered since 27 January 2009.

These applications were submitted using the Decentralised Procedure (DCP), with the IT as Reference Member State (RMS), and Greece as the only Concerned Member State (CMS).

The active substance Zolpidem tartrate belongs to the pharmacotherapeutic group of Hypnotics and Sedatives, ATC code: N05CF02.

Zolpidem tartrate is an imidazopyridine which preferentially binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.

One bioequivalence study was submitted for the 10 mg strength to support the related application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of the product.

Regarding the statement on GMP for the active substance a suitable declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

The RMS and CMS considered that the applications could be approved at the end of procedure on 19 April 2022. After a subsequent national phase, licences were granted in the IT on 08 July 2022.

# QUALITY ASPECTS

* 1. **Introduction**

Each orodispersible tablet contains 5 mg or 10 mg zolpidem tartrate as the active ingredient. Other ingredients consist of the pharmaceutical excipients polacrillin potassium, mannitol, lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, aspartame, magnesium stearate and blackcurrant flavour (consisting of flavouring substances and preparations, natural flavouring substance, maize maltodextrin, glyceryl triacetate, triethyl citrate, sulphite ammonia caramel, moisture).

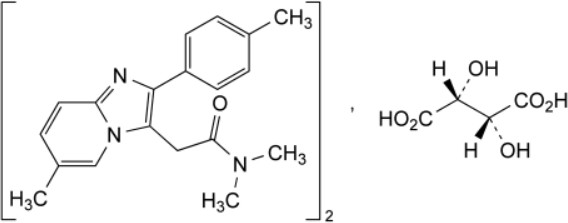
Both strengths of the finished product are packed into aluminium-aluminium blisters (blister foil components - base foil: PVC-OPA-aluminium- PVC; lidding foil: aluminium-PVC) in pack sizes of:

* + - 5mg strength tablets: 14, 28, 30 and 56 orodispersible tablets;
    - 10 mg strength tablets: 28 and 30 orodispersible tablets.

# Drug Substance

INN: Zolpidem tartrate

Chemical name: Bis[*N*,*N*-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3- yl]acetamide] (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Structural formula:

Molecular formula: C42H48N6O8 Molecular mass: 765 g/mol

Appearance: White or almost white, hygroscopic, crystalline powder.

Solubility: Zolpidem Tartrate is slightly soluble in water, sparingly soluble in methanol and practically insoluble in Methylene chloride.

Zolpidem tartrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, zolpidem tartrate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

# II.3. Medicinal Product Pharmaceutical Development

A quality by design (QbD) approach was used to develop Zolpidem Tartrate Orodispersible Tablets, generic version of marketed reference listed drug STILNOX ® tablets 10 mg marketed by Sanofi – Aventis, France. The development was performed for 10 mg strength and the same qualitative and quantitative composition was used to scale down the formulation for 5 mg strength.

Comparative *in-vitro* dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of potassium polacrillin which is compliant with the United States Pharmacopeia and the National Formulary (USP-NF) and the blackcurrant flavour which complies with a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

# Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing processes has been validated at commercial scale batch sizes for 10 mg strength and at pilot scale batch sizes for 5 mg strength. The marketing authorisation holder (MAH) has committed to conclude the process validation on commercial scale batch sizes for 5 mg strength and an interim validation report has been provided (validation studies on commercial scale were ongoing).

# Finished Product Specifications

The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specifications.

# Stability of the product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 4 years with no special temperature storage conditions. The medicinal product should be stored in the original package in order to protect it from light and moisture.

# II.4 Discussion on chemical, pharmaceutical and biological aspects

The quality characteristics of Sonirem, 5 mg and 10 mg Orodispersible tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk.

# NON-CLINICAL ASPECTS

* 1. **Introduction**

As the pharmacodynamic, pharmacokinetic and toxicological properties of zolpidem tartrate 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.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

# Pharmacology

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

# Pharmacokinetics

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

# Toxicology

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

# Ecotoxicity/environmental risk assessment (ERA)

Since Sonirem is intended for generic substitution, this will not lead to an increased environmental exposure. An environmental risk assessment is therefore not deemed necessary**.**

# Discussion on the non-clinical aspects

There are no objections to the approval of these applications from a non-clinical viewpoint.

# CLINICAL ASPECTS

* 1. **Introduction**

The clinical pharmacology of zolpidem tartrate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of zolpidem tartrate.

Based on the data provided, Sonirem can be considered bioequivalent to Stilnox 5mg and 10 mg Film-Coated Tablets (Sanofi Aventis, France).

# Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence study:

# STUDY

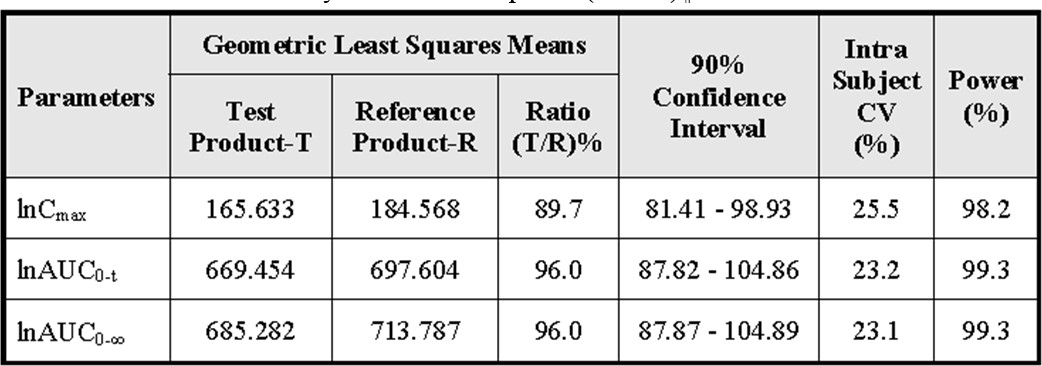
An open-label, balanced, randomised, single oral dose, two-treatment, two-sequence, two-period, crossover, bioequivalence study of the applicant’s test product Zolpidem Athena tartrate 10 mg Orodispersible tablets (Athena Drug Delivery Solutions Pvt. Ltd., India) versus the reference Stilnox 10 mg, comprimé pelliculé sécable (Sanofi Aventis France) in healthy, adult, subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 10 mg tablet) of the test or reference product.

The main difference between the treatments was that the test product was an orodispersible formulation while the reference was a tablet. The methods for administration of the study medications and recording of the time of administrations were acceptable. Other aspects of the design were also acceptable including the safety evaluations**.**

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 10 days. The pharmacokinetic results are presented below:

# Table: Summary statistics for the pharmacokinetic parameters for zolpidem is presented below:



Cmax maximum plasma concentration

AUC0-t area under the plasma concentration-time curve from zero to t hours AUC0-∞ area under the plasma concentration-time curve from zero to ∞ hours

# Study Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for zolpidem lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr\*\*). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Stilnox 10 mg, comprimé pelliculé sécable (Sanofi Aventis France).

As the 5 mg strength test product meets the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 10 mg tablet strength can be extrapolated to the 5 mg strength tablet.

# Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

# Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

# Clinical safety

No new safety data were submitted and none are required.

# Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, 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 Sonirem, 5 mg and 10 mg Orodispersible tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, arelisted below:

**Summary of safety concerns**

Important identified risks: None

Important potential risks: None

Missing information: None

Routine pharmacovigilance and risk minimisation are proposed for all safety concerns.

# Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

# User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

# 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 zolpidem tartrate is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the marketed reference products and their risk-benefit balance is considered similar and positive.