LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Edluar
(zolpidem tartrate)

SE/H/1046/01-02/DC

This module reflects the scientific discussion for the approval of Edluar. The procedure was finalised at 2012-06-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Meda AB has applied for a marketing authorisation for Edluar, sublingual tablets, 5 and 10 mg claiming essential similarity to Stilnoct, 10 mg film coated tablets marketed in Denmark by Sanofi-Aventis. The product contains zolpidem tartrate as active substance. For approved indications see the Summary of Product Characteristics. The reference products used in the bioavailability/bio-equivalence studies are Stilnoct/Stilnox, 10 mg film coated tablets marketed by Sanofi-Aventis in Sweden and Germany.

II. QUALITY ASPECTS

II.1 Introduction

Edluar is presented in the form of sublingual tablets containing 5 mg and 10 mg of zolpidem tartrate. The excipients are mannitol, silicified microcrystalline cellulose, silica colloidal anhydrous, croscarmellose sodium, saccharin sodium and magnesium stearate. The sublingual tablets are packed in aluminium/aluminium blisters.

II.2 Drug Substance

Zolpidem tartrate has a monograph in the Ph Eur.

Zolpidem tartrate is a white or almost white crystalline powder which is slightly soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride. The structure of zolpidem tartrate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on stereochemistry is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Edluar sublingual tablet is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, only the local oral tolerability of 5 and 10 mg zolpidem tartrate sublingual tablets has been studied in an *in vivo* animal model. The product caused no local irritation when administered to the cheek pouches of Syrian hamsters daily for a period of 28 days.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

During the course of development, three formulations of Edluar (OX22), namely Formulation I (FI), Formulation II (FII) and the Final Commercial Product (FCP) in two dose strengths (5 mg and 10 mg), were developed and used in initial exploratory and pivotal clinical studies.

To support the application five bioequivalence/bioavailability studies were submitted.

OX22-001: A three-way cross-over study comparing Formulation I (5 mg and 10 mg) and Stilnoct, film-coated tablet 10 mg (UK reference product).

OX22-004: A two-way cross-over study comparing Formulation II (10 mg) and Formulation I (10 mg).

OX22-005: A Three-way cross-over study investigating the effect of food on Formulation II (10 mg) and bioequivalence with Ambien, 10 mg, film-coated tablets (US reference product).

OX22-008: A two-way cross-over study comparing Formulation II (10 mg) and Final Commercial Product (10 mg).

3289: A two-way cross-over study comparing Final Commercial Product (10 mg) with Stilnox, 10 mg, film-coated tablets (German reference product).

Bioequivalence has been demonstrated between Edluar FCP and the reference product Stilnox under fasting conditions (Study 3289). Both AUC and C_{max} were within the conventional acceptance range of 80-125%. Under fasting conditions, t_{max} of both products were similar: median t_{max} (range) was 1.00 h (0.25-3.50 h) and 0.75 h (0.50-3.00 h) for Edluar and Stilnox, respectively. Also t½ were similar for the two formulations.

After administration of Edluar with a high fat meal, a small food-effect was observed: C_{max} was approximately 34% and AUC 12% lower and compared to administration in the fasted state. Median t_{max} was prolonged from 1.00 h to 1.75 h. Edluar is recommended to not be taken with or immediately after a meal.

Dose-proportionality between Edluar 5 mg and 10 mg sublingual tablets has been demonstrated.

Bioequivalence for AUC and C_{max} has been demonstrated between FII (used in clinical study OX22-006) and the FCP. For FI (used in clinical study OX22-002) bioequivalence with the FCP was demonstrated for C_{max}, whereas AUC was slightly higher for FI (ratio: 1.17, 90% CI: 1.08-1.27). However, given that bioequivalence has been demonstrated between Edluar FCP and Stilnox, the bridging to the clinical studies is of less importance.

The pharmacokinetic documentation is sufficient.

IV.2 Pharmacodynamics

Formulation I was used in a single-dose efficacy and safety study in 21 healthy volunteers (OX22-002). This study showed an earlier onset of the sleep-inducing effect of zolpidem sublingual tablets (Edluar) of approximately six minutes relative to Stilnoct. Formulation II was used in a single-dose efficacy and safety study in 73 patients (OX22-006). This study showed that zolpidem sublingual tablets (Edluar) at the 10 mg dose shortened latency to persistent sleep by approximately ten minutes, relative to standard tablets containing 10 mg (Ambien). The final formulation was used in a local tolerance and safety study in 60 patients (OX22-007).

Formulation I and II were used in the clinical safety and efficacy studies. The bridging between the Edluar FCP and these early formulations is considered to be sufficient.

IV.3 Discussion on the clinical aspects

This product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data. Three studies with Edluar, sublingual tablets, 5 and 10 mg (Study OX22-002, OX22-006 and OX22-007) were included in the application providing sufficient support of the hypnotic effect of zolpidem tartrate when given as sublingual tablets.

The applicant has demonstrated, in proprietary studies and analysis of public domain literature, that the safety of Edluar, sublingual tablets will be comparable to the reference medicinal product when given for short-term treatment of insomnia. Short-term treatment has been translated by the Applicant into a time-interval of a few days to two weeks with a maximum of four weeks including tapering off, at appropriate dose.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference regarding the PIL content to Zolpidem Mylan (SE/H/310/01/II/17) and regarding layout to Tasmar (EMEA/H/C/000132, FUM 017) . The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Edluar, sublingual tablets, 5 and 10 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Edluar, sublingual tablets, 5 and 10 mg was successfully finalised on 2012-06-14.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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