

Public Assessment Report Scientific discussion

Zolpmitriptan Teva, 2.5 mg and 5 mg, orodispersible tablets (zolmitriptan)

SE/H/867/01-02/DC

This module reflects the scientific discussion for the approval of Zolmitriptan Teva, 2.5 mg and 5 mg, orodispersible tablets. The procedure was finalised at 26 January 2010. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Teva Sweden AB has applied for a marketing authorisation for Zolmitriptan Teva, 2.5 mg and 5 mg, orodispersible tablets claiming essential similarity to Zomig Rapimelt, 2.5 mg orodispersible tablet marketed in Sweden by AstraZeneca. The product contains zolmitriptan as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Zomig Rapimelt, 5 mg, orodispersible tablets and Zomig, 5 mg, tablets marketed by AstraZeneca in Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Zolmitriptan Teva, 2.5 mg and 5 mg, orodispersible tablets is presented in the form of tablets containing 2.5 mg and 5.0 mg of Zolmitriptan. The excipients are colloidal anhydrous silica, Starlac (lactose monohydrate and maize starch), mannitol, croscarmellose sodium, citric acid (Anhydrous powder), sodium bicarbonate, aspartame, magnesium stearate, Orange flavour durarome (sucrose, maltodextrin, natural flavours, soya lecithin, and silicon dioxide).

The tablets are packed in/filled in aluminium blister.

II.2 Drug Substance

Zolmitriptan does not have a monograph in the Ph Eur.

Zolmitriptan is a white, crystalline powder which is poorly soluble in water. The structure of Zolmitriptan has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, and chirality, 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/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

Zolmitriptan Teva, 2.5 mg and 5 mg, orodispersible is formulated using excipients described in the current Ph Eur, except for Starlac and Orange flavour durarome which are controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin/has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility and particle size.

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, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Zolmitriptan is rapidly and well absorbed, the absolute bioavailability is approximately 40%. When given as a single dose in healthy volunteers, AUC and C_{max} showed approximate dose proportionality. There was no food interaction for the originator product, and therefore no restriction with respect to food in the labelling. Zolmitriptan is cleared principally by hepatic metabolism, and one of the metabolites (N-desmethyl-zolmitriptan) is pharmacologically active and is likely to contribute to the therapeutic activity. The mean elimination half-life is around 3 h.

To support the application, the applicant has submitted as report one bioequivalence study (2008-1758). It was a single dose bioequivalence study with Zolmitriptan Teva 5 mg orodispersible tablets versus Zomig Rapimelt 5 mg orodispersible tablets and Zomig 5 mg tablets. The results are shown below.

Based on the submitted bioequivalence study Zolmitriptan Teva 5 mg orodispersible tablet is considered bioequivalent with Zomig 5 mg orodispersible tablet (AstraZeneca AB). The results of study 2008-1758 with 5 mg orodispersible tablet formulation can be extrapolated to the other strengths (2.5 mg), according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacokinetic zolmitriptan parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range)

Treatment	AUC_{0-t} ng*h/ml	AUC_{0-∞} ng*h/ml	C_{max} ng/ml	t_{max} h
A (Zolmitriptan Teva 5 mg without water)	49.771 $\pm$ 15.199	52.708 $\pm$ 16.681	8.763 $\pm$ 3.071	3.00 0.67-5.00
B (Zolmitriptan Teva 5 mg with water)	48.135 $\pm$ 17.137	51.229 $\pm$ 19.151	8.528 $\pm$ 2.426	1.50 0.50-3.33
C (Zomig Rapimelt 5 mg without water)	50.068 $\pm$ 15.673	53.244 $\pm$ 17.197	8.927 $\pm$ 2.933	2.67 0.33-5.00
*Ratio (90% CI) A vs C	99.59 (92.10-107.70)	99.11 (91.82-106.97)	96.90 (87.95-106.77)	-
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration				

**calculated based on ln-transformed values*

IV.2 Discussion on the 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 clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed, but an acceptable bridging to a test for a similar product has been made.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Zolmitriptan Teva, 2,5 mg and 5 mg, orodispersible tablet is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Zolmitriptan Teva, 2.5 mg and 5 mg, orodispersible tablets was successfully finalised on 26 January 2010.

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)