LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Topiramat Bluefish
Topiramate

SE/H/782/01-04/DC

This module reflects the scientific discussion for the approval of Topiramat Bluefish. The procedure was finalised at 2009-12-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Bluefish Pharmaceuticals AB has applied for a marketing authorisation for Topiramat Bluefish, film-coated tablets, 25mg, 50 mg, 100 mg and 200 mg claiming essential similarity to Topimax, film-coated tablets, 25 mg, 50 mg, 100 mg and 200 mg marketed in Sweden by Janssen-Cilag AB. The product contains topiramate as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Topamax, tablets marketed by Janssen-Cilag Ltd. in UK.

II. QUALITY ASPECTS

II.1 Introduction

Topiramat Bluefish is presented in the form of film-coated tablets of four strengths containing 25, 50, 100 and 200 mg of topiramate respectively. The excipients are lactose monohydrate, microcrystalline cellulose, pregelatinised starch, croscarmellose sodium, magnesium stearate and tablet coatings containing hypromellose, titanium dioxide, macrogol and iron oxides. The tablets are packed in HDPE bottles or aluminium/aluminium blisters.

II.2 Drug Substance

The drug substance topiramate is not described in a Ph. Eur. monograph.

Topiramate is a white or almost white powder. It is soluble in methanol and in 0.1N aqueous NaOH solution and slightly soluble in water. The structure has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality has been presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The specifications and control tests for topiramate are adequately drawn up. The analytical methods applied are suitably described and validated.

Stability studies have been performed with the drug substance and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Topiramat Bluefish film-coated tablets are formulated using excipients described in the current Ph. Eur., except for the iron oxides in the tablet coatings of the three higher tablet strengths. Iron oxides are described in NF. The only ingredient of animal origin is lactose monohydrate, for which compliance with the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) is certified.

The development and the manufacturing process of the drug product have been sufficiently described.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis results show that the finished products meet the specifications proposed.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25°C.

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

Topiramate is absorbed to a high degree when given orally and the absorption is not affected by food. Topiramate is mainly eliminated renally but metabolism occurs and is increased when topiramate is given together with enzyme inducing antiepileptic agents. Elimination half life is around 21 hours, and volume of distribution 0.55-0.8 l/kg.

To support the application, the applicant has submitted the report of one randomized, two-treatment, two-period, two-sequence single dose bioequivalence study of Topiramate Bluefish 200 mg tablets compared with Topamax 200 mg tablets, Janssen-Cilag Ltd, from the UK market. The study was performed in healthy subjects under fasting conditions. Based on the submitted bioequivalence study Topiramate Bluefish 200 mg tablets are considered bioequivalent with Topamax 200 mg tablets, see results below.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Topiramate Bluefish 200 mg	**179 847 (30 936)**	**5181 (743)**	**2.25 (0.5-4.0)**
Topamax 200 mg	**182 053 (31 675)**	**5238 (898)**	**2.38 (0.5-4.0)**
***Ratio (90% CI)**	**0.99 (0.97-1.01)**	**0.99 (0.96-1.03)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
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 been performed and is acceptable.

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 Topiramat Bluefish, film-coated tablets, 25mg, 50 mg, 100 mg and 200 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Topiramat Bluefish, film-coated tablets, 25mg, 50 mg, 100 mg and 200 mg was successfully finalised on 2009-12-16.

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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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