LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Donepezil Mylan, 5 mg and 10 mg, film-coated tablet
Donepegen, 5 mg and 10 mg, film-coated tablet
Penzondil, 5 mg and 10 mg, film-coated tablet
Donepezil Generics, 5 mg and 10 mg, film-coated tablet
Donepe, 5 mg and 10 mg, film-coated tablet
Donezil, 5 mg and 10 mg, film-coated tablet

Applicant: Merck NM AB
(donepezil hydrochloride)

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SE/H/0768/001-002/DC

This module reflects the scientific discussion for the approval of Donepezil Mylan and duplicates. The procedure was finalised at 2009-02-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Merck NM has applied for a marketing authorisation for Donepezil Mylan, Donepegen, Penzondil, Donepezil Generics, Donepe, and Donezil, 5 mg and 10 mg, film-coated tablets claiming essential similarity to Aricept 5 mg and 10 mg film-coated tablets marketed in the EU by Pfizer". The product contains donepezil hydrochloride as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Aricept 10 mg tablets marketed by Pfizer PGM, France in UK.

II. QUALITY ASPECTS

II.1 Introduction

Donepezil Mylan, Donepegen, Penzondil, Donepezil Generics, Donepe, and Donezil 5 mg and 10 mg, film-coated tablets are presented in the form of tablets containing 5 mg or 10 mg of donepezil hydrochloride which corresponds to 4,56 mg or 9,12 mg donepezil . The excipients are lactose monohydrate, maze starch, hydroxypropylcellulose, microcrystalline cellulose, magnesium stearate, HPMC, titanium dioxide, and polyethylene glycol. The tablets are packed in blister of PVC/PVDC/Al and in PP bottles with PE cap.

II.2 Drug Substance

Donepezil hydrochloride does not have a monograph in the Ph Eur. Information on donepezil hydrochloride has been supplied in the form of an ASMF.

Donepezil hydrochloride is a white, crystalline powder. The aqueous solubility is pH dependent. The structure of donepezil hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism 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

Donepezil Mylan, Donepegen, Penzondil, Donepezil Generics, Donepe, and Donezil 5 mg and 10 mg, film-coated tablets is formulated using excipients described in the current Ph Eur. Lactose monohydrate is the only material of anomal origin used and satisfactory TSE statement are provided.
The product development has taken into consideration the physico-chemical characteristics of the active substance.

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

Following an oral dose of donepezil, maximal plasma concentrations are reached within 3 to 4 hours. There was no food interaction for the originator product and therefore no restriction with respect to food in the labelling. Donepezil is eliminated as unchanged drug though renal excretion and by metabolism to several metabolites, whereof 6-O-desmetyldonepezil, has similar pharmacological activity as the parent drug. On the basis of in vitro studies, the metabolism of donepezil has been indicated to be mediated by the isoenzymes CYP3A4 and CYP2D6 (to less extent). The terminal half-life is approximately 70 hours, and steady-state is reached within 3 weeks following the start of the therapy. Donepezil displays linear pharmacokinetics.

To support the application, the applicant has submitted as report one bioequivalence study (Final report BS562), in which Aricept film-coated tablets 10 mg are compared with Donemerck film-coated tablets 10 mg following a single dose under fasting conditions. Bioequivalence was based on measurements of the parent compound, which is considered sufficient as the active metabolite is not considered to significantly contribute to the net activity and the pharmacokinetic system is considered linear.

Based on the submitted bioequivalence study Donemerck film-coated tablets 10 mg are considered bioequivalent with Aricept film-coated tablets 10 mg. The results of study BS562 with 10 mg formulation can be extrapolated to other strengths (5 mg), according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

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 SPC, package leaflet and labelling are 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 Donepezil Mylan, Donepegen, Penzondil, Donepezil Generics, Donepe, and Donezil, 5 mg and 10 mg, film-coated tablets are recommended for approval.

VI. APPROVAL

The Decentralised procedures for Donepezil Mylan, Donepegen, Penzondil, Donepezil Generics, Donepe, and Donezil, 5 mg and 10 mg, film-coated tablets were successfully finalised on 2009-02-27.

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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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