IPAR

IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Donepezil Niche 5mg & 10mg

Orodispersible Tablets

Donepezil Hydrochloride

PA 1063/46/1-2

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted marketing authorisations for Donepezil Niche 5 mg and 10 mg orodispersible tablets, from Niche Generics Limited on 20th January 2012 for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

This application for a marketing authorisation was submitted in accordance with Article 10 of Directive 2001/83/EC and is referred to as a generic application. Donepezil Niche 5 mg and 10 mg orodispersible tablets have the same qualitative and quantitative composition in terms of the active substance as Aricept 5 mg and 10 mg film-coated tablets.

This product is licensed for supply subject to medical prescription which may not be renewed. It can be advertised to the healthcare professions only.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie

Name of the product	Donepezil Niche 5 mg & 10 mg orodispersible tablets
Name(s) of the active substance(s) (INN)	DONEPEZIL HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	N06DA02
Pharmaceutical form and strength(s)	5 mg & 10 mg orodispersible tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA 1063/46/1-2
Marketing Authorisation Holder (MAH)	Niche Generics Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Donepezil Niche 5 mg and 10 mg orodispersible tablets

II.2 Drug substance

The active substance is donepezil hydrochloride, an established active substance not described in the European or British Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The product is presented as orodispersible tablets with the following composition:

Substance
Donepezil hydrochloride 5 mg or 10 mg per tablet

Excipients
Mannitol
Silicified microcrystalline cellulose
Low-substituted hydroxypropyl cellulose
Sucralose (micronised powder)

Sodium stearyl fumarate
Orange Flavouring
Yellow iron oxide (10 mg strength only)

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The finished product specification is based on the pharmacopoeial monograph for orodispersible tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented in aluminium/aluminium triple layer (OPA/aluminium/PVC) laminate blisters, packed within a cardboard carton.

Evidence has been provided that the aluminium foil and the aluminium laminate comply with the appropriate Ph. Eur. requirements and EU legislation for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years when stored at or below 25ºC and in the original package in order to protect from moisture.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Donepezil Niche 5 mg and 10 mg orodispersible tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European and Irish markets since November 1996. Preclinical data have

been superseded by clinical experience and therefore no preclinical assessment report is available.

III.2 Pharmacology

Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is *in vitro* over 1000 times more potent an inhibitor of this enzyme than of butylcholinesterase, an enzyme that is present mainly outside the central nervous system.

Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3-4 hours. Pharmacokinetics are linear over the dose range 1-10 mg. It circulates approximately 96% bound to human plasma proteins, mainly albumins. It is metabolised by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. The elimination half life is about 70 hours. It is both excreted in the urine intact and extensively metabolised to four major metabolites, two of which are known to be active, and a number of minor metabolites.

As this is a generic product no additional environmental impact is expected.

IV CLINICAL ASPECTS

IV.1 Introduction

Donepezil is a well known active substance with established efficacy and tolerability.

The content of the Summary of Product Characteristics (SPC) approved during the national procedure is in accordance with that accepted for the reference product Aricept 5 mg & 10 mg Tablets, marketed by Pfizer Healthcare Ireland.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Donepezil Niche is compared with the pharmacokinetic profile of the reference product Aricept Evess.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Donepezil 10 mg orodispersible tablets, by Niche Generics, were compared to the reference product Aricept Evess 10 mg orodispersible tablets, by Eisai. Based on the pharmacokinetic parameters of active substance, the reference tablet Aricept and test tablet Donepezil Niche are bioequivalent with regard to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 5 mg film-coated tablets are dose proportional with the 10 mg orodispersible tablets. The pharmacokinetic profile of the active substance and is linear in the dosage range. The results of the bioequivalence study performed with the 10 mg orodispersible tablets therefore apply to the other strengths.

Risk Management Plan

No additional risk management or risk minimisation plans have been submitted or are required, apart from those measures necessary for routine pharmacovigilance. This is acceptable.

PSUR submission schedule

Donepezil is part of the Heads of Medicines Agency (HMA) Periodic Safety Update Report (PSUR) Worksharing procedure, with a 3 year PSUR submission schedule and a data-lock point of November 2011. As such, the next procedure is expected soon after the conclusion of this authorisation procedure, and the applicant commits to update their license in line with the Core Safety Profile resulting from the PSUR-WS procedure.

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Aricept marketed by Pfizer.

The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption: Maximum plasma levels are reached approximately 3 to 4 hours after oral administration. Plasma concentrations and area under the curve rise in proportion to the dose. The terminal disposition half-life is approximately 70 hours, thus, administration of multiple single-daily doses results in gradual approach to steady-state. Approximate steady-state is achieved

within 3 weeks after initiation of therapy.

Once at steady-state, plasma donepezil hydrochloride concentrations and the related pharmacodynamic activity show little variability over the course of the day. Food did not affect the absorption of donepezil hydrochloride.

Distribution: Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil in not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of 14C-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Metabolism/Excretion: Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of 14C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30%), 6-O-desmethyl donepezil (11% - only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyl donepezil (7%) and the glucuronide conjugate of 5-O-desmethyl donepezil (3%). Approximately 57% of the total administered radioactivity was recovered from the urine (17% as unchanged donepezil), and 14.5% was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination. There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites.

Plasma donepezil concentrations decline with a half-life of approximately 70 hours.

Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil hydrochloride. The pharmacokinetics of donepezil has not been formally studied in healthy elderly subjects or in Alzheimer's or vascular dementia patients. However mean plasma levels in patients closely agreed with those of young healthy volunteers.

Patients with mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean Cmax by 39%.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Donepezil Niche 5 mg and 10 mg orodispersible tablets are a generic form of Aricept. Aricept is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. As donepezil takes part in the HMA PSUR-WS procedure, subsequent PSURs will follow that schedule.

The IMB, on the basis of the data submitted considered that Donepezil Niche demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. This licence will be subject to review and renewal in 5 years.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

VI REVISION DATE

January 2012