CBG MEB

Public Assessment Report

Scientific discussion

Navazil 5 mg and 10 mg, film-coated tablets

(donepezil hydrochloride)

NL/4393/001-002/MR

Date: 3 July 2018

This module reflects the scientific discussion for the approval of Navazil 5 mg and 10 mg, film-coated tablets. The procedure was finalised on 20 October 2011 with Germany as RMS (DE/H/3099/001/DC). The second RMS was Finland. The current RMS, after a second switch, is the Netherlands (NL/H/4393/001-002/MR). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Navazil 5 mg and 10 mg, film-coated tablets from Navamedic ASA.

The product is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

A comprehensive description of the indications and posology is given in the SmPC.

This procedure concerns a generic application claiming essential similarity with the innovator product Aricept which has been registered in the United Kingdom by Eisai Ltd since 14 February 1997 through mutual recognition procedure UK/H/0182/001.

The reference member states (RMS) of the initial procedure was Germany and the concerned member states (CMS) involved in this procedure were Belgium, Denmark, Finland, Iceland, Luxembourg, Norway and Sweden. The role of the RMS was first transferred to Finland and on 19 March 2018 the role of the RMS was transferred to the Netherlands.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Navazil 5 mg film-coated tablets are white to off-white coloured, round and biconvex and debossed with ‘5’ on one side and a break line on the other side. Each film-coated tablet contains 5 mg donepezil hydrochloride, equivalent to 4.56 mg of donepezil.

Navazil 10 mg film-coated tablets are peach coloured, round, biconvex and debossed with ‘10’ on one side and a break line on the other side. Each film-coated tablet contains 10 mg donepezil hydrochloride, equivalent to 9.12 mg of donepezil.

The film-coated tablets are packed in HDPE bottles with a child resistant PP closure and induction sealing wad, PVC/Alu blisters and OPA/Alu//PVC/Alu.

The excipients are:
Tablet core - maize starch, lactose monohydrate, microcrystalline cellulose and magnesium stearate
Tablet coating – hypromellose, macrogol 6000, talc, titanium dioxide (E-171) and only for the 10 mg strength yellow and red iron oxide (E172).

II.2 Drug Substance

Donepezil hydrochloride is not included in a pharmacopeia. An Active Substance Master File (ASMF) from the active substance manufacturer has been submitted. The chemical-pharmaceutical documentation and expert report are of sufficient quality in view of the present European regulatory requirements. The control tests and specifications for drug substance product are adequately drawn up. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The retest period of 24 months is justified by long-term data.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches. The batch analysis results show that the finished products meet the specifications

proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. A shelf-life of 36 months for the drug product is supported by 24 month long term data.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Navazil has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made

III. NON-CLINICAL ASPECTS

Donepezil is a substance with well-known pharmacodynamic, pharmacokinetic and toxicological properties that have been adequately summarised in the non-clinical overview. The instructions on use of the active substance during pregnancy and lactation and the preclinical safety data contained in the proposed SmPC and section “Pregnancy and breast-feeding” of the PL are identical to the texts approved for the reference product Aricept and are hence acceptable. There are no further objections from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

As donepezil hydrochloride is a widely used, well-known active substance, no further studies are required for this application and the applicant provides none. Overview based on literature review should be, thus, appropriate.

To support the application, the applicant has submitted one bioequivalence study.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, two- way crossover bioequivalence study Navazil 10 mg tablets of Torrent Pharmaceuticals Ltd., India versus Aricept 10 mg tablets of Pfizer GmbH, Germany in healthy adult male subjects under fasting conditions.

The mean pharmacokinetic parameters of donepezil for reference Product-A and test product-B for 19 subjects are summarised in the following tables.

Table-A: Descriptive statistics of formulation means for donepezil (n=19)

Parameter (Units)	Mean ± SD (Un-transformed data)	
	Reference Product-A	Test Product-B
Tmax (h)*	3.000	3.000
Cmax (ng / mL)	18.553 ± 3.7769	18.675 ± 4.6370
AUC0-72h (ng.h / mL)	482.303 ± 92.5884	471.168 ± 86.7718

*Tmax is represented in median value.

Table-B: Geometric least squares mean, ratios and 90% confidence interval for donepezil (n=19)

Parameters (Units)	(ln-transformed) Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Test Product-B	Reference Product-A	Ratio (B / A)%	
Cmax (ng / mL)	17.834	18.130	98.4	92.97-104.08%
AUC0-72h (ng.h/mL)	457.923	467.698	97.9	95.78-100.09%

The test product-B Navazil, when compared with the reference product-A Aricept, meets the bioequivalence criteria with respect to the rate and extent of absorption of donepezil as set in the protocol.

As all conditions defined in section 5.4 of the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" are fulfilled the results of the bioequivalence study with the 10 mg strength can be extrapolated to the lower dose strength.

The bioanalytical method showed an acceptable performance.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Aricept. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

An assessment of User Testing was performed in a parallel European procedure (DE/H/2811/001-002/DC) which was overall considered adequate. As the tested package leaflet (by Torrent) appears to be the same as the package leaflet for Donepezil hydrochlorid Aspen 5/10 mg filmtabletten, except for the product name, the readability test report is regarded as acceptable. In addition, the applicant has confirmed that the package leaflets are identical in design and layout.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Navazil 5 mg and 10 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Aricept 5 mg and 10 mg, tablets. Aricept is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Navazil with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 20 October 2011. The transfer to the Netherlands was finalised on 19 March 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
DE/H/3099/IB/001/G	– Changes in the manufacturing process of the active substance; minor change to the restricted part of an Active Substance Master File – Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance; more than 10-fold increase compared to the currently approved batch size – Change to in-process tests or limits applied during the manufacture of the active substance; addition of a new in-process test and limits	No	05-01-2012	Approved	-
DE/H/3099/1-2/IA/002	Change to importer, batch release arrangements and quality control testing of the finished product; replacement or addition of a site where batch control testing takes place	No	11-06-2012	Approved	-
DE/H/3099/1-2/IB/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Article 45 or 46 of Regulation (EC) No 1901/2006; Implementation of wording agreed by the competent authority	Yes	24-10-2012	Approved	-
DE/H/3099/1/IA/004	Change in the batch size (including batch size ranges) of the finished product; up to 10-fold compared to the originally approved batch size	No	21-02-2013	Approved	-
DE/H/3099/1/IB/005/G	– Change in the (invented) name of the medicinal product; for nationally authorised products – Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier) – Other variation	No	21-05-2013	Approved	-
DE/H/3099/1-2/IA/006	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; primary packaging site	No	14-10-2013	Approved	-
DE/H/3099/1-2/IA/007	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; Secondary packaging site	No	20-09-2013	Approved	-
FI/H/0859/IA/008/G	– Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier) – Change to importer, batch release arrangements and quality control testing of the finished product; Replacement or addition of a manufacturer responsible for importation and/or batch release; not including batch control/testing – Other variation	No	22-11-2015	Approved	-

FI/H/0859/IB/009/G	– Other variation – Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance; addition of a new specification parameter to the specification with its corresponding test method – Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance; minor changes to an approved test procedure – Change in the shelf-life or storage conditions of the finished product; as packaged for sale (supported by real time data)	Yes	15-04-2016	Approved	-
FI/H/0859/1-2/IA/010	Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)	No	23-06-2016	Not Approved	Not all the documents needed are submitted
FI/H/0859/1-2/IA/011	Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)	No	02-09-2016	Approved	-
FI/H/0859/IB/012/G	– Change in the manufacturer of a starting material/ reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier; other variation – Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance; tightening of specification limits – Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance; minor changes to an approved test procedure	No	09-09-2016	Approved	-
FI/H/0859/1-2/IB/013	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/ biosimilar medicinal products following assessment of the same change for the reference productsubstance; minor changes to an approved test procedure; implementation of changes for which no new additional data is required to be submitted by the MAH	Yes	22-12-2017	Approved	-