

**PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands**

**Donepezilhydrochloride Ipca 5 mg and 10 mg film-coated tablets  
Ipca Produtos Farmaceuticos Unipessoal Lda, Portugal**

**donepezil hydrochloride**

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2626/001-002/DC  
Registration number in the Netherlands: RVG 111596-111597**

**10 July 2013**

Pharmacotherapeutic group:	anti-dementia drugs, anticholinesterases
ATC code:	N06DA02
Route of administration:	oral
Therapeutic indication:	mild to moderately severe Alzheimer's dementia
Prescription status:	prescription only
Date of authorisation in NL:	30 June 2013
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

## I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Donepezilhydrochloride Ipca 5 mg and 10 mg film-coated tablets from Ipca Produtos Farmaceuticos Unipessoal Lda. The date of authorisation was on 30 June 2013 in the Netherlands.

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 SPC.

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 inhibitor of this enzyme than of butyrylcholinesterase, an enzyme that is present mainly outside the central nervous system.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Aricept 5 and 10 mg film-coated tablets which has been registered in the UK by M/s Eisai Ltd. and Pfizer Ltd. UK since 14 February 1997. In addition reference is made to Aricept authorizations in the individual member states. The drug product Aricept has never been registered in the Netherlands, its application was withdrawn in 1997. Reference is made to the innovator product registered in the UK as a so-called European reference product.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Aricept 10 mg film-coated tablets, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

## II SCIENTIFIC OVERVIEW AND DISCUSSION

### II.1 Quality aspects

#### **Compliance with Good Manufacturing Practice**

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

#### **Active substance**

The active substance is donepezil hydrochloride, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.) or the British Pharmacopoeia (BP); a monograph has been published in the U.S. Pharmacopoeia (USP\*). It is a white to off white, crystalline powder, which is soluble in water, methanol, and chloroform, and sparingly soluble in acetic acid. Donepezil hydrochloride is a racemic compound and exhibits polymorphism. The manufacturer produces Form I consistently.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

#### Manufacturing process

The manufacturing process was sufficiently described. Donepezil hydrochloride is synthesized in eight stages including crystallization, condensation, reduction, isolation, formation purification. The proposed starting materials are redefined and considered acceptable, and all questions were addressed satisfactory.

#### Quality control of drug substance

The drug substance specification is an in-house specification in accordance with European guidance and the USP monograph. The specifications are acceptable in view of the route of synthesis. The MAH has added a specification for particle size, which is discussed in relation to the drug product. Analytical methods are adequately described and validated. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

#### Stability of drug substance

Stability data on the active substance have been provided for seven production-scale batches, stored at 25°C/60%RH (12-60 months), 2-8°C (36-60 months, five batches), 30°C/65%RH (6 months, three batches) and 40°C/75% RH (6 months, three batches). No trends were observed in any of the parameters at 25°C/60%RH and 30°C/65%RH. In view of the provided stability data, a retest period of 60 months is justified. The storage conditions is acceptable (Do not store above 25°C).

\* *Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

### **Medicinal Product**

#### Composition

Donepezilhydrochloride Ipca 5 mg is a white to off white, circular, biconvex, film coated tablet, embossed with "C" on one side and "7" on other side. Each 5 tablet contains 5 mg donepezil hydrochloride, equivalent to 4.56 mg of donepezil.

Donepezilhydrochloride 10 mg is a yellow colored, circular, biconvex, film-coated tablet, embossed with "C" on one side and "6" on other side. Each tablet contains 10 mg donepezil hydrochloride, equivalent to 9.12 mg of donepezil.

The film-coated tablets are packed in clear PVDC coated PVC/Aluminium blisters.

The excipients are:

*Tablet core* – lactose, microcrystalline cellulose, dried maize starch, hydroxy propyl cellulose, sodium stearyl fumarate.

*Film-coating* – HPMC/Hypromellose, titanium dioxide (E171), purified talc, polyethylene glycol (6000), ferric(iron) oxide yellow E172 (10 mg only).

The two strengths are dose proportional.

#### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. A direct compression method was chosen as the manufacturing process. The pharmaceutical development of the product has been adequately performed. The development of the clinical batches is discussed, comparative dissolution profiles at different pHs were provided, and the discriminative power of the dissolution medium is demonstrated. Dissolution profiles were comparable to the innovator for both strengths. Essential similarity between the test product and the innovator product Aricept® has been demonstrated on quality grounds.

#### Manufacturing process

The drug product was manufactured by sifting, blending, lubrication, compression, film coating and packaging. It is a straightforward standard process, the provided in-process controls are deemed acceptable. The manufacturing process has been adequately validated according to relevant European guidelines for batch sizes ranging from minimum to maximum size.

#### Control of excipients

All excipients are tested in accordance with their respective Ph.Eur. monograph or in-house specification. The specifications are acceptable.

#### Quality control of drug product

The drug product specifications includes tests for description, identification (retention time, titanium dioxide, iron oxide yellow), average weight, uniformity of dosage units, assay, dissolution, related substances, loss on drying and microbiological quality.

The shelf-life specifications are the same as the release specification, with the exception of the limit for related substances. The specification is considered acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two batches of each tablet strength, demonstrating compliance with the release specifications.

#### Stability of drug product

Stability data on the active drug product has been provided on two minimum sized batches of each tablet strength, stored at 25°C/60% RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear PVDC coated PVC/Aluminium blister pack. No specific changes or patterns are noted at any of the conditions in any of the parameters. A photostability study is performed in conformity with ICH topic Q1B. Sensitivity to light was not shown. The proposed shelf-life of 2 years can be accepted as well as the proposed storage condition (This medicinal product does not require any special storage conditions).

#### Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose is the only excipients of animal origin. the lactose is sourced from healthy animals under the same conditions as milk collected for human consumption and the calf rennet used for production of raw

material which is in accordance with Public Statement EMEA/CPMP/571/102. Therefore the TSE risk for the lactose used can be considered negligible.

## II.2 Non-clinical aspects

This product is a generic formulation of Aricept, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

### Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of donepezil hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

Donepezil hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Donepezilhydrochloride Ipca 10 mg (Ipca Produtos Farmaceuticos Unipessoal Lda, Portugal) is compared with the pharmacokinetic profile of the reference product Aricept 10 mg tablets (M/s Eisai Ltd., UK).

### *The choice of the reference product*

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

### *Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male and female subjects, aged 19-24 years. Each subject received a single dose (10 mg) of one of the 2 donepezil formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 31 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 32.5, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 6, 8, 10, 12, 16, 24, 48, 144, 240, 288 and 360 hours after administration of the products.

The use of the higher strength is agreed as this is in accordance to the Guideline on the Investigation of Bioequivalence. The study design is acceptable. The duration of the sampling and wash-out period are sufficient to measure pharmacokinetics parameters adequately considering the  $t_{max}$  and long half-life of around 80 hours.

### *Analytical/statistical methods*

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

### *Results*

Twenty-three (23) subjects completed the study. One subject was withdrawn as he was tested positive for benzodiazepines at check-in in Period II, 3 subjects and another 3 subjects were withdrawn due to vomiting in Period I and II, respectively. The blood samples of the withdrawn subjects were analysed but not included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of donepezil under fasted conditions.

Treatment N=23	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	722 $\pm$ 203	754 $\pm$ 207	17.7 $\pm$ 5.2	2 (1 – 4.5)	80 $\pm$ 22
<b>Reference</b>	704 $\pm$ 173	737 $\pm$ 178	17.1 $\pm$ 4.3	2.3 (1 – 8)	78 $\pm$ 25
<b>*Ratio (90% CI)</b>	1.02 (0.97 – 1.07)	1.01 (0.97 – 1.06)	1.03 (0.98 – 1.09)	--	--
<b>CV (%)</b>	10.2	9.5	9.5	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of donepezil under fasted conditions, it can be concluded that Donepezilhydrochloride 10 mg and Aricept 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Donepezil may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of donepezil. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

#### Safety

There were 8 mild adverse events (*i.e.* vomiting, nausea) with the test (3) and reference drug (5). Donepezil is known to cause such adverse events. There were no deaths, serious or significant adverse events reported during the course of the study. Overall, the test and reference drugs were well tolerated.

#### Biowaiver

A biowaiver for the 5 mg strength was granted based on the following reasons:

- Both strengths (10 mg and 5 mg) of donepezil hydrochloride are manufactured by the same manufacturer and manufacturing process.
- The qualitative composition of both strengths is the same.
- Both strengths are quantitatively dose-proportional
- Donepezil is a BCS class I drug with linear pharmacokinetics.
- The *in-vitro* dissolution profile is similar between the 10 mg strength used in bioequivalence study and the additional 5 mg strength.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

#### Risk management plan

Donepezil hydrochloride was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of donepezil hydrochloride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

#### **Product information**

##### SPC

The SPC is harmonised with the text for other donepezil generics registered through decentralised procedures.

##### Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. As a result of the pilot testing no changes to either the leaflet or the questionnaire were deemed necessary. This was also the case after the first round of testing. After two rounds of user testing, 90% of the subjects were able to locate the requested information and gave the correct answer. As a result, no changes were deemed necessary to the patient information leaflet of Donepezilhydrochloride Ipca.

Overall, it can be concluded that the readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Donepezilhydrochloride Ipca 5 mg and 10 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Aricept 5 and 10 mg film-coated 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other donepezil containing products.

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 Donepezilhydrochloride Ipca 5 mg and 10 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 5 April 2013. Donepezilhydrochloride Ipca 5 mg and 10 mg film-coated tablets were authorised in the Netherlands on 30 June 2013.

The date for the first renewal will be: 5 April 2018.

The following post-approval commitments have been made during the procedure:

#### Quality - medicinal product

- The MAH committed that comparative dissolution profile testing will be undertaken on the first three production batches.
- The MAH committed that a holding time study will be carried out on the initial production scale batches.
- The MAH committed to determine holding times of the common blend, tablet cores and coated tablets on the initial product scale batches.



## List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C <sub>max</sub>	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t <sub>1/2</sub>	Half-life
t <sub>max</sub>	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached