IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dozept 5 mg film-coated tablets
Donepezil hydrochloride
PA0711/141/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) 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 HPRA 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 HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number DE/H/5622/001-002 with Germany as RMS. The responsibility of RMS was transferred to Ireland on 19 July 2023 under procedure number IE/H/1285/001-002
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0711/141/001-002
Marketing Authorisation Holder: Rowex Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The DE public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for *Donepezil-HCl HEXAL5 /10 mg Filmtablettenin the treatment of mild to moderately severe Alzheimers dementia is approvable.*

These applications were submitted under Article 10.1 of Directive 2001/83 EC (as amended), for *Donepezil-HClHEXAL5 /10mgFilmtabletten*. They have been shown to be generic medicinal products of the originator products Aricept 5mg and 10mg Tablets (Marketing Authorisation Holder: Eisai Limited, UK) which were granted licences on 14.02.1997 in the UK.

Donepezil hydrochloride, a piperidine derivative, is a centrally active, reversible inhibitor of acetylcholinesterase. A deficiency of acetylcholine caused by selective loss of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus is recognized as one of the early pathophysiologic features of Alzheimer's disease associated with memory loss and cognitive deficits. Since the resultant cortical deficiency of this neurotransmitter is believed to account for some of the clinical manifestations of mild to moderate dementia, enhancement of cholinergic function with an anticholinesterase agent, such donepezil, is one of the pharmacologic approaches to treatment. Due to the fact that widespread degeneration of multiple central neuronal systems eventually occurs in patients with Alzheimer's disease, the potentially beneficial effects of anticholinesterase agents would diminish as the disease process advances and fewer cholinergic neurons remain functioning.
No new preclinical studies were conducted, which is acceptable given that the applications were based on essential similarity to products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

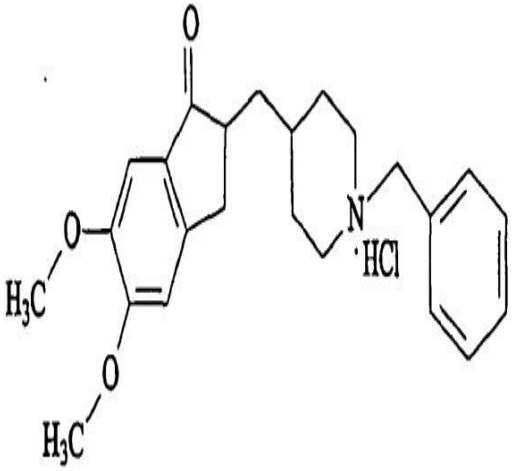
After changing the RMS, Germany is the new RMS. The former procedure number was UK/H/1146/001-002/DC.

II. QUALITY ASPECTS

S. Activesubstance

Nomenclature:

INN: Donepezil hydrochloride
Chemical name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4- piperidinyl]methyl]-1*H*-inden-1-one, hydrochloride
Structure:



Molecular formula: C24H30ClNO3
Molecular weight: 415.95 g/mol
Characteristics: White to off-white or slightly yellow crystalline powder
Solubility: Donepezil Hydrochloride is freely soluble in chloroform, dichloromethane and in methanol, soluble in water, sparingly soluble in ethanol, n-butanol and in acetonitrile and very slightly soluble in acetone.
Polymorphism: Donepezil Hydrochloride is known to exist in different polymorphic forms including hydrates, anhydrates, crystalline and amorphous form.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.
The drug substance donepezil hydrochloride is not the subject of BP or Ph.Eur monographs. An appropriate specification is provided for the active substance donepezil hydrochloride.
Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Active donepezil hydrochloride is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.

P. Medicinal product
Other Ingredients
Other ingredients consist of pharmaceutical excipients namely microcrystalline cellulose, lactose monohydrate, maize starch and magnesium stearate. All ingredients within the tablet body comply with relevant Ph Eur monographs.

The tablet coating contains: polyvinyl alcohol, talc, titanium dioxide (E171), macrogol 3350, soya lecithin and (iron oxide yellow (E172)- only present in 10mg strength). All the ingredients within the tablets coating comply with their relevant Ph Eur monographs with the exception of lecithin which complies with USNF (US National Formulary) and JP (Japanese Pharmacopoeia).
Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose none of the excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption.

Pharmaceutical development

The objective of formulation was to develop generic film-coated tablets bioequivalent to the reference product, Aricept 5mg and 10mg Tablets.
The objectives of the development programme were to develop a formula and a manufacturing process for *Donepezil-HCl HEXAL5 /10 mg Filmtabletten*, to produce tablets with the following
1) comparable dissolution profile to the brand
2) bioequivalent to the brand
3) meet all physical and chemical specifications for the dosage form in general and for this product.

Dissolution and impurity profiles
Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the
release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
*Donepezil-HClHEXAL5/10mgFilmtabletten*are packaged either in clear polyvinyl chloride (PVC)/aluminium blister packs or in high density polyethylene (HDPE) containers with a (polypropylene) PP or HDPE screw cap containing desiccant. Blister pack presentation is available in pack sizes of 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100, 100x1 or 120 film-coated tablets and the bottle presentation is available in pack sizes of 100 tablets. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies have been performed on the six batches of 5mg strength and seven batches of 10mg strength. All batches are packaged in the proposed commercial packaging. Stability testing is performed according to the relevant ICH guidelines.
Based on the results of the stability studies, the applicant has proposed a shelf life of 18 months and 6months after first opening of the HDPE bottle, with storage conditions of "Do not store above
25°C". These are acceptable.

SPC,PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
The grant of marketing authorisation is recommended.

III. NON-CLINICAL ASPECTS

No new non-clinical data were supplied with this application and none are required. Clinical experience with Donepezil HCL overrides the need for further preclinical data. The non-clinical overview provides a satisfactory review of the relevant non-clinical pharmacological and toxicological literature.

IV. CLINICAL ASPECTS

Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview dated 14.05.2007 has been written by a suitably qualified person with relevant experience in the pharmaceutical industry. The report refers to 66 publications up to 2006.
The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Clinical study reports
To support the application, the applicant has submitted a single bioequivalence study: an open label, single dose, randomised, 2 way study of crossover design, performed under fasting conditions. The
study was performed at the 10mg dose strength.

Biowaiver
The multiple strengths exemption criterion for linear pharmacokinetics over the therapeutic range is met. The company's clinical expert has provided the following justification for studying the 10mg strength only, rather than both strengths:

a. The pharmacokinetics are linear
b. The qualitative composition is the same
c. The ratio between active substance and the excipients in both strengths of the test product is the same
d. The dissolution rate of the highest strength of the test product in-vitro is similar to that of the lower strength, and the dissolution rate of both of the strengths of the test product in vitro is similar to
the dissolution rates of the corresponding strengths of the reference product.

A review of the PK characteristics of donepezil indicates that absorption is predictable and it appears unlikely that the conclusion of bioequivalence would be any different if the 5mg dose had also been studied. It is normally considered that the highest dose strength is the most discriminatory for the purposes of bioequivalence testing, which is the strength which has been tested here. The confidence intervals for the bioequivalence parameters of the presented studies are within the required limits by a substantial margin.
In conclusion the use of the 10mg strength only for the bioequivalence studies has been adequately justified and the results of Study 2006-24-FTA-1 with the 10mg formulation can be extrapolated to other strength 5mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98.

Pharmacokinetic studies
Study2006-24-FTA-1

Study design
A comparative, randomised, two-way, two-period, single dose crossover study performed in fasting subjects. Healthy, fasting, male volunteers, aged 23-44 years, were randomised to receive a single dose of 10mg orally of either the applicant's test product or the reference product donepezil.
The randomisation scheme was balanced for sequence and appears random.
Serum drug levels were followed for 72 hours following dosing and the schedule was appropriate for accurate determination of AUC0-72 and Cmax. The washout period between phases was sufficiently long at 21 days.

Test and reference products
Reference: Aricept 10mg Film Coated Tablets (Donepezil Hydrochloride) (Eisai GmbH, Germany.)
Test: *Donepezil-HCl HEXAL 10 mg Filmtabletten* (Donepezil Hydrochloride) (HEXAL AG, Germany)

Analytical methods
Plasma samples were analysed to quantify the concentration of donepezil using a validated LC/MS/MS bioanalytical method. The validation report has been provided. The lower limit of quantification was 0.250 ng/ml for donepezil and 50.0 pg/ml for 6-O-desmethyldonepezil.

Statistical methods
ANOVA for AUC0-72, Cmax. Non-parametric for Tmax. Analysis of sequence/period effects.

Results
Table 1. Pharmacokinetic parameters for parent drug (non-transformed values; arithmetic mean ± SD, tmax , median, range).

Parameter	**TEST**				**REFERENCE**				**F (treatment)**	**P**
Cmax	**Geometric LS Mean**	**Arithmetic Mean**	**S.D.**	**C.V.**	**Geometric LS Mean**	**Arithmetic Mean**	**S.D.**	**C.V.**		

(ng/mL)	15.607	16.235	4.593	28.3	16.463	17.210	5.514	32.0	1.96	N.S.
Tmax (hours)*		3.50	0.88	23.1		3.00	0.97	30.6	102	< 0.005
AUC0-72 (ng·h/mL)	413.494	433.494	131.939	30.4	414.692	432.908	125.612	29.0	0.05	N.S.

*median is presented and test statistic of treatment effect is based on Wilcoxon's.
N.S. = not significant

Table 2. Pharmacokinetic parameters for parent drug (log-transformed values).

Parameter	**Ratio(%)**	**90 %Confidence Limits (%)**		**Intrasubject C.V. (%)**
		Lower	**Upper**	
Cmax(ng/mL)	94.80	89.42	100.50	9.65
AUC0-72(ng·h/mL)	99.71	95.25	104.38	7.56

Table 3. Pharmacokinetic parameters for 6-O-desmethyldonepezil (non-transformed values; arithmetic mean ± SD, tmax , median, range).

Parameter	**TEST**				**REFERENCE**				**F (treatment)**	**P**
	Geometric LS Mean	**Arithmetic Mean**	**S.D.**	**C.V.**	**Geometric LS Mean**	**Arithmetic Mean**	**S.D.**	**C.V.**		
Cmax (pg/mL)	73.2	74.9	14.6	19.5	74.7	79.5	29.9	37.6	0.29	N.S.
Tmax (hours)*		4.00	0.95	24.0		3.75	2.46	56.2	14.5	N.S.
AUC0-72 (pg·h/mL)	261.9	405.1	262.0	64.7	187.9	365.6	358.7	98.1	0.06	N.S.

*median is presented and test statistic of treatment effect is based on Wilcoxon's.
N.S. = not significant

Table 4. Pharmacokinetic parameters for 6-O-desmethyldonepezil (log-transformed values).

Parameter	**Ratio(%)**	**90 %Confidence Limits (%)**		**Intrasubject C.V. (%)**
		Lower	**Upper**	
Cmax(pg/mL)	98.07	79.76	120.57	19.36
AUC0-72(pg·h/mL)	139.37	66.59	291.66	77.47

These results are within conventional bioequivalence criteria, with 90% confidence intervals between 80-125% for the parent drug only. It is noted that the data for the 6-O-Desmethyl metabolite are not within conventional bioequivalence acceptance criteria. Displaying activity equal to that of the parent drug, this metabolite is to be found in concentrations up to 20% that of the parent drug. There is no evidence to suggest entero-hepatic recycling or accumulation.

From the data presented, there would seem to be two possible explanations for what is seen:

1. Statistical - 90% CIs are very wide and include unity so there may be no formulation difference at all.
2. True formulation difference. The estimated 5% lower Cmax for the test product indicates a slightly slower drug delivery, resulting in a greater proportion being metabolised pre-systemically into the active metabolite, resulting in bioinequivalence for the metabolite.

Either way, the active metabolite cannot be considered to contribute greatly to the activity of this product. There have been a number of other European procedures for donepezil products whereby the metabolites have not been assayed at all. Overall, it is considered that this product fulfils conventional bioequivalence acceptance criteria.

Pharmacokinetic conclusion

Based on the submitted bioequivalence study *Donepezil-HCl HEXAL 10 mg Filmtabletten* are considered bioequivalent with Aricept 10mg Film Coated Tablets (Donepezil Hydrochloride) (Eisai GmbH, Germany.).
The results of Study 2006-24-FTA-1 with the 10mg formulation can be extrapolated to the other strength, 5mg, according to conditions in Note for Guidance on the Investigation of Bioavailability
and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Post marketing experience

*Donepezil-HClHEXAL5/10mgFilmtabletten*have a well-recognised efficacy and an acceptable level of safety in the indications approved for Donepezil, and corresponding products have been
widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

Benefit -Risk Assessment

The application contains an adequate review of published clinical data and the bioequivalence has been demonstrated for 10mg tablets. The results could be extrapolated to 5mg tablets. Approval is recommended from the clinical point of view.

SUMMARY OF PRODUCT CHARACTERISTICS

The SPCs are in line with those of the reference products and are satisfactory.

PATIENTINFORMATION LEAFLET

The PIL is satisfactory.

LABELLING

Medically satisfactory,

DISCUSSION

The application contains an adequate review of published clinical data. Bioequivalence has been demonstrated for 10mg tablets. The results could be extrapolated to 5mg tablets. The clinical safety and efficacy of donepezil hydrochloride is well established as it has been used extensively in clinical practice.

The SPCs are in line with those of the reference products and are satisfactory. The PIL and labelling are medically satisfactory.

CONCLUSIONS

The grant of marketing authorisations is recommended

V. OVERALL CONCLUSIONS

QUALITY

The important quality characteristics of *Donepezil-HClHEXAL5/10mgFilmtabletten*are well- defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's *Donepezil-HCl HEXAL 10 mg Filmtabletten* and the reference product Aricept 10mg Tablets (Eisai Limited). As these products meet the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to the 5mg strength tablets. No new or unexpected safety concerns arise from this application. The SPC, PIL and labelling are satisfactory.

RISKBENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with donepezil hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

The application is approved. For intermediate amendments see current product information.

VI. REVISION DATE

25 April 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From DE/H/5622/001-002 to IE/H/1285/001-002	N/A	19 July 2023	N/A