COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Galantamine Aurobindo Retard 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard (galantamine hydrobromide)

NL/H/6282/001-003/DC

Date: 18 June 2025

This module reflects the scientific discussion for the approval of Galantamine Aurobindo Retard 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard. The procedure was finalised at 21 March 2018 in Portugal (PT/H/1829/01-03/DC). After a transfer on 17 April 2025, the current RMS is the Netherlands. For information on changes after the finalisation 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 agreed in granting a marketing authorisation for Galantamine Aurobindo Retard 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard, from Aurobindo Pharma B.V.

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

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

This decentralised application concerns a generic version of galantamine, under the trade name Galantamina Ritisca in PT (RMS).

The originator product is Reminyl 8, 16 and 24 mg, prolonged-release capsule, hard, which is registered in the Portugal by Janssen-Cilag Farmacêutica, Lda., since December 06th, 2004.

The marketing authorization was granted on 12-04-2018 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph and the Marketing Authorisation Holder is Generis Farmacêutica, S.A.

With Portugal as the Reference Member State in this Decentralized Procedure, Generis Farmacêutica, S.A.(Portugal) is applying for the Marketing Authorisation for Galantamine in ES, NL and UK.

II. QUALITY ASPECTS

II.1 Introduction

Prolonged-release capsule, hard.

Galantamine Aurobindo Retard 8 mg, prolonged-release capsules, hard:
White opaque, Size “1” hard gelatin capsules with inscription “A” over the cap & “8” over the body containing one white to off white round, biconvex mini tablet.

Galantamine Aurobindo Retard 16 mg, prolonged-release capsules, hard:
Pink opaque, Size “1” hard gelatin capsules with inscription “A” over the cap & “16” over the body containing two white to off white round, biconvex mini tablets.

Galantamine Aurobindo Retard 24 mg, prolonged-release capsules, hard:
Caramel opaque, Size “1” hard gelatin capsules filled with inscription “A” over the cap & “24” over the body containing three white to off white round, biconvex mini tablets.

- The active substance is galantamine.

  Each prolonged-release capsule contains 8 mg galantamine (as hydrobromide).
  Each prolonged-release capsule contains 16 mg galantamine (as hydrobromide).
  Each prolonged-release capsule contains 24 mg galantamine (as hydrobromide).

- The excipients are

  Capsule Fill: Cellulose, microcrystalline (Grade -102), talc, hydroxy propyl cellulose, silica, colloidal anhydrous, magnesium Stearate

  Capsule Shell:

  8 mg: Titanium Dioxide (E171), sodium lauryl sulfate, gelatin

  16 mg: Titanium Dioxide (E171), iron oxide red (E172), sodium lauryl sulfate, gelatin

  24 mg: Titanium Dioxide (E171), iron oxide red (E172), iron oxide yellow (E172) sodium lauryl sulfate, gelatin

  Printing ink: Shellac, black iron oxide (E172)

Galantamine Aurobindo Retard, prolonged-release capsules, hard are available in clear PVC/PE/PVdC-Alu foil blister pack.

Pack sizes:
Blister packs: 28 and 30 prolonged-release capsules, hard

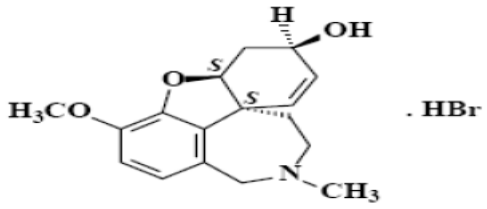
Not all pack sizes may be marketed.

II.2 Drug Substance

Nomenclature

European Pharmacopoeia monograph name	:	Galantamine Hydrobromide
Recommended International Nonproprietary Name (rINN)	:	Galantamine Hydrobromide
Chemical Name(s)	:	(4*aS*,6*R*,8*aS*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro-[3*a*,3,2-*ef*][2]benzazepin-6ol hydrobromide *(or)* 6*H*-Benzofuro[3*a*,3,2-*ef*][2]benzazepin-6ol,4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-hydrobromide,(4*aS*,6*R*,8*aS*)-
Laboratory Code*	:	GO
Other Nonproprietary Names(s)		
USAN, BANM	:	Galantamine Hydrobromide
Chemical Abstract Service (CAS) Registry Number	:	[1953-04-4]

Structure

Structural formula	:	 . HBr
Molecular formula	:	$C_{17}H_{21}NO_3.HBr$
Molecular weight	:	368.27
Isomerisation/Chirality	:	Galantamine has three chiral centres and it could exist only in two enantiomeric pairs (Four stereo isomers) due to steric constraints such as (-)-Galantamine (4*aS*,6*R*,8*aS*), (+)-Galantamine (4*aR*,6S,8*aR*), (-)Epigalantamine (4*aS*,6S,8*aS*) and (+)Epigalanthamine (4*aR*,6*R*,8*aR*). The naturally occurring and therapeutically active isomer is (-)-Galanthamine, which is having the configuration of 4*aS*,6*R*,8*aS*.

General Properties

Description	:	White or almost white crystalline powder
Solubility	:	Sparingly soluble in water, practically insoluble in anhydrous ethanol, soluble in 0.1N sodium hydroxide.
Polymorphism	:	Polymorphic forms of Galantamine Hydrobromide are not known in the literature.
Therapeutic category	:	Cholinesterase Inhibitor
Melting point	:	246 – 247°C
Other Properties		
Specific optical rotation $[\alpha]^{20}_{D}$ (c=2, in water, on dried basis)	:	Between -90° and -100°
pH	:	Between 4.0 and 5.5

Quality control of drug substance

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to galantamine hydrobromide 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 of drug substance

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 3 years is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product
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.
The proposed shelf-life of 36 months without any special storage condition for the drug product packed in PVC/PE/PVDC-Alu blisters is considered acceptable.

Pack sizes: 28 or 30

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of galantamine are well known. As galantamine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Galantamine Aurobindo Retard 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 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

Bioequivalence studies

To support this application, the Applicant has submitted as report three bioequivalence studies conducted in healthy subjects under the following conditions: single-dose in fasting conditions (Study nº. 419-15), single-dose in fed conditions (Study nº. 420-15) and steady-state in fed conditions (Study nº. RP.15.1151) with the strength of Galantamine 8 mg prolonged-release capsules, which are entitled:

Study nº. 419-15: *"An Open Label, Randomized, Two-Treatment, Two-Sequence, Two period, Crossover, Single-Dose, Oral Bioequivalence Study of Galantamine Prolonged Release Capsules 8 mg (Test) of Aurobindo Pharma Limited, India and Reminyl® XL Prolonged Release Capsules 8 mg (Reference) of Shire Pharmaceuticals Limited, UK in Healthy, Adult Human Subjects Under Fasting Conditions."*

Study nº. 420-15: *"An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose, oral bioequivalence study of Galantamine Prolonged Release Capsules 8 mg (test) of Aurobindo Pharma Limited, India and Reminyl® XL Prolonged Release Capsules 8 mg (reference) of Shire Pharmaceuticals Limited, UK in healthy, adult human subjects under fed conditions."*

Study nº. RP.15.1151: *"An open label, randomized, two-treatment, two-sequence, two-period, crossover, steady state, bioequivalence study of Galantamine Prolonged Release Capsules 8 mg (Test) of Aurobindo Pharma Limited, India and Reminyl XL Prolonged Release Capsules 8 mg (Reference) of Shire Pharmaceuticals Limited, UK in 40 healthy, adult, human subjects under fed conditions."*

Both products (Test and Reference) are oral prolonged-release capsules (multiple-unit dosage form). According to the current "Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms" (EMA/CPMP/EWP/280/96 Corr1) for the demonstration of bioequivalence between two prolonged release (multi-unit) formulations for oral administration the following studies are required: a single-dose BE study under fasting conditions; a single-dose BE study under fed conditions using a high-fat meal; and a multiple-dose BE study. Therefore, in principle, the three bioequivalence studies submitted are enough to support this application. The multiple-dose (steady-state) study was performed under fed conditions because the SmPC of the Reference product recommends that galantamine prolonged-release capsules be preferably taken with food.

Although the Applicant wishes to get marketing authorization of generic Galantamine prolonged-released capsules for 8 mg, 16 mg & 24 mg strengths, the BE studies were performed on the 8 mg product, rather than on the highest strength (24 mg), but it was justified by Applicant as follows: "The bioequivalence study should in general be conducted at the highest strength. Selection of a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. The

recommended starting dose of galantamine prolonged release capsules for patients is 8 mg/day for 4 weeks and then should be titrated to the initial maintenance dose of 16 mg/day".

Biowaiver
A biowaiver for 16 mg and 24 mg strengths is requested by Applicant.

The Bio-equivalence study was carried out on Galantamine 8mg Prolonged-release Capsules. Based on acceptable Bio-equivalence study for Galantamine 8mg Prolonged-release Capsules, a bio-waiver is requested for Galantamine 16mg and 24mg Prolonged-release Capsules as per following considerations:

1. *Galantamine 8mg, 16mg & 24mg Prolonged-release Capsules are manufactured by the same manufacturer i.e. Aurobindo Pharma Limited (Unit VII) and using the same manufacturing process.*
2. *Galantamine pharmacokinetics of Galantamine prolonged release capsules are dose proportional within the studied dose range of 8 mg to 24 mg once-daily in elderly and young age groups. [UK-SmPC of Galantamine prolonged-release capsules].*
3. *The qualitative composition of Galantamine 16mg & 24mg prolonged release capsules is the same as that of Galantamine 8mg prolonged release capsules.*
4. *Galantamine 16mg & 24mg prolonged release capsules are dose proportional to that of Galantamine 8mg prolonged release capsules.*
5. *The dissolution profile of Galantamine 16mg & 24mg prolonged release capsules is similar to Galantamine 8mg prolonged release capsules. The dissolution profile of Galantamine 16mg prolonged release capsules (Batch No. GHSB15001), Galantamine 24mg prolonged release capsules (Batch No. GHSC15001) was compared to Galantamine 8mg prolonged release capsules, (Batch No. GHSA15001, i.e. Test Batch used in Bio-equivalence Study) in different media viz. 0.1N HCl, pH-4.5 Acetate buffer and pH 6.8 Phosphate buffer and was found similar.*

The conditions required for a biowaiver for the strengths of Galantamine 16 mg and 24 mg prolonged-release capsules (Aurobindo Pharma Limited, India) seem to be fulfilled, based on the demonstration of bioequivalence with the strength of 8 mg.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Galantamine Aurobindo Retard 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard is considered bioequivalent with Reminyl 8 mg, 16 mg e 24 mg Prolonged-release capsule, hard

IV.2 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Galantamine Aurobindo Retard 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard.

IV.3 Discussion on the clinical aspects

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' authorized 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. This generic product can be used instead of its reference product

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Galantamin Pharmathen (DE/H/2875/01-03/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Galantamine Aurobindo Retard 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

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
PT/H/1829/001-3/IB/001	Change in the (invented) name of the medicinal product for Nationally Authorised Products	Yes	19-08-2019	Approved	N.A.
PT/H/1829/001-3/IB/002	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation	Yes	04-04-2021	Approved	N.A.
PT/H/1829/001-3/IA/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 Articles 45 or 46 of Regulation 1901/2006SmPCSmPC • Implementation of wording agreed by the competent authority	Yes	21-04-2021	Approved	N.A.
PT/H/1829/001-3/R/001	Renewal	No	07-12-2022	Approved	N.A.
PT/H/1829/001-3/IB/004	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 product • Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	05-12-2022	Approved	N.A.

PT/H/1829/001-3/IA/005	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer	No	02-02-2023	Approved	N.A.
PT/H/1829/001-3/IA/006	Deletion of manufacturing sites (including 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)).	Yes	26-05-2023	Approved	N.A.
PT/H/1829/001-3/IA/007	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.	No	17-07-2024	Approved	N.A.

	• Updated certificate from an already approved manufacturer				