COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atomoxetine HCl Aurobindo 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg hard capsules

(atomoxetine hydrochloride)

NL/H/4741/001-007/DC

Date: 24 September 2019

This module reflects the scientific discussion for the approval of Atomoxetine HCl Aurobindo. The procedure was finalised at 6 June 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CMS	Concerned Member State
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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Atomoxetine HCl Aurobindo 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules from Aurobindo Pharma B.V.

Atomoxetine HCl Aurobindo is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist. Diagnosis should be made according to current DSM criteria or the guidelines in ICD.

In adults, the presence of symptoms of ADHD that were pre-existing in childhood should be confirmed. Third-party corroboration is desirable and Atomoxetine HCl Aurobindo should not be initiated when the verification of childhood ADHD symptoms is uncertain. Diagnosis cannot be made solely on the presence of one or more symptoms of ADHD. Based on clinical judgment, patients should have ADHD of at least moderate severity as indicated by at least moderate functional impairment in 2 or more settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

Additional information for the safe use of this product
A comprehensive treatment programme typically includes psychological, educational and social measures and is aimed at stabilising patients with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

Pharmacological treatment is not indicated in all patients with this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity of the patient's symptoms and impairment in relation to the patient's age and the persistence of symptoms.

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

This decentralised application concerns a generic version of atomoxetine 10 mg/18 mg/25 mg/40 mg/60 mg/80 mg/100 mg hard capsules manufactured by Aurobindo Pharma Limited (India) under Atomoxetine HCl Aurobindo trade name.

This marketing authorisation application is submitted under Directive 2001/83/EC Article 10.1 in cross-reference to the non-clinical and clinical data supporting the European marketed formulation, Strattera, available for clinical use and marketed since more than 10 years in most countries worldwide. The originator product is Strattera, 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules by Eli Lilly Nederland B.V., registered in the

Netherlands on 15 December 2004 (for 10 mg, 18 mg, 25 mg, 40 mg and 60 mg dosages) and 20 August 2008 (for 80 mg and 100 mg dosages).

The concerned member states (CMS) involved in this procedure were the Czech Republic, Germany, Spain, Poland, and Romania.

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

II. QUALITY ASPECTS

II.1 Introduction

Atomoxetine HCl Aurobindo is a hard gelatin capsule filled with white to off-white powder

- 10 mg - off-white opaque/off-white opaque, capsules and imprinted with 'AT' on off-white opaque cap and '10' on off-white opaque body with black ink.
- 18 mg - golden opaque/off-white opaque, capsules and imprinted with 'AT' on golden opaque cap and '18' on off-white opaque body with black ink.
- 25 mg - blue opaque/off-white opaque, capsules and imprinted with 'AT' on blue opaque cap and '25' on off-white opaque body with black ink.
- 40 mg - blue opaque/blue opaque, capsules filled and imprinted with 'AT' on blue opaque cap and '40' on blue opaque body with black ink.
- 60 mg - blue opaque/golden opaque, capsules and imprinted with 'AT' on blue opaque cap and '60' on golden opaque body with black ink.
- 80 mg - brown opaque/off-white opaque, capsules and imprinted with 'AT' on brown opaque cap and '80' on off- white opaque body with black ink.
- 100 mg - brown opaque/brown opaque, capsules and imprinted with 'AT' on brown opaque cap and '100' on brown opaque body with black ink.

The hard capsules are available in PVC/PE/PVdC- Aluminium foil blister packs.

The excipients are:

- The capsules contain pregelatinised starch (maize starch), and simethicone emulsion (30%)
- The capsule cap contains titanium dioxide (E171), sodium lauryl sulphate., iron oxide yellow (E172) (for 18 mg, 80 mg and 100 mg), indigo carmin (E132) (for 25 mg, 40 mg and 60 mg), iron oxide red (E172) (for 80 mg and 100 mg), gelatin, purified water.
- The capsule body contains titanium dioxide (E171), sodium lauryl sulphate., indigo carmin (E132) (for 40 mg only), iron oxide yellow (E172) (for 60 mg and 100 mg), iron oxide red (E172) (for 100 mg only), gelatin, purified water.
- The printing ink (Black) contains shellac (E904) and black iron oxide (E172)

II.2 Drug Substance

Table 1. Nomenclature

Recommended International Nonproprietary Name (rINN)	:	Atomoxetine Hydrochloride
Compendial Name *(European Pharmacopoeia)*	:	Atomoxetine Hydrochloride
Chemical Name(s)	:	(3R)-*N*-Methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine hydrochloride (or) (R)-(-)-*N*-Methyl-γ-(2-methylphenoxy)-benzenepropanamine hydrochloride
Product code	:	AT
Other Nonproprietary Name(s)		
BAN, USAN	:	Atomoxetine Hydrochloride
Chemical Abstracts Service (CAS) Registry Number (RN)	:	[82248-59-7]

Table 2. Structure

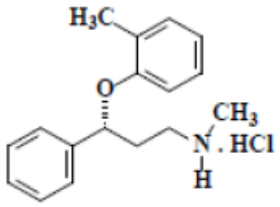
Structural formula	:	
Molecular formula	:	$C_{17}H_{21}NO.HCl$
Molecular weight	:	291.82
Chirality		Atomoxetine hydrochloride has one chiral center and hence exists as two isomers. The (R)-isomer having (-) rotation is the marketed form.

Table 3. General properties

Description	:	White or almost white powder
Solubility	:	Sparingly soluble in water, soluble in anhydrous ethanol, practically insoluble in heptane
Polymorphism	:	Atomoxetine Hydrochloride exhibits polymorphism. Atomoxetine hydrochloride manufactured by Aurobindo is polymorphic Form "A"
Specific Optical Rotation $[\alpha]_D^{25}$ (c=1, in Methanol, on dried basis)	:	Between -38.0° to -44.0°
pKa	:	10.13
Log P[1]	:	3.81
Hygroscopicity	:	Non hygroscopic in nature

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to atomoxetine hydrochloride 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 proposed retest period of 36 months is justified.

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.

The proposed shelf-life of 24 months without any special storage conditions for the drug product packed in clear PVC/PE/PVdC - Aluminium foil blister pack is considered acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atomoxetine HCl Aurobindo 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

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Atomoxetine HCl Aurobindo 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

This product is a generic formulation of Strattera which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Atomoxetina 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH has submitted as report a single dose bioequivalence study (Study No. 0718-16) under fasting conditions:

"An open label, randomized, two treatment, two sequence, two period, cross over, single-dose, oral bioequivalence study of Atomoxetine capsules 60 mg (test) and Strattera (Atomoxetine) Capsules 60 mg (reference) of Eli Lilly and Company Limited, UK in healthy, adult, human subjects under fasting condition."

Based on the EMA - Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/ QWP/1401/98 Rev.1), a single-dose comparative bioavailability study is adequate to demonstrate bioequivalence between test and reference formulations for oral administration (immediate-release formulations with systemic action).

The choice of atomoxetine 60 mg for the conduct of bioequivalence study is justified on pharmacokinetic and safety grounds. Although there is no specific guidance from EMA on atomoxetine, the FDA guidance recommends that "60 mg is studied because higher doses may cause unacceptable side-effects in normal healthy subjects". Furthermore, the linear kinetics and high solubility of the active substance also supports the Applicant's decision.

In conclusion: the choice of Atomoxetine 60 mg for the conduct of bioequivalence study is acceptable.

According to CPMP Guidelines on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1, January 2010), if an application concerns several strengths of the active substance a bioequivalence study with only one strength may be acceptable, provided that all of the following conditions are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the strengths are quantitatively proportional i.e. the ratio between active substance and the excipients is the same, or, in the case of preparations containing a low concentration of the active substance, the ratio between the amounts of excipients is similar.
- The dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Based on the Guideline on the Investigation of Bioequivalence (CPMP/EWP/ QWP/1401/98 Rev.1), all conditions for the biowaiver for additional strengths are fulfilled.

IV.3 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 Atomoxetine HCl Aurobindo.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Strattera. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Atomoxetine 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (Caduceus Pharma Limited) which was approved through a decentralised procedure (procedure no: UK/H/6038/001-007/DC). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atomoxetine HCl Aurobindo 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules. Strattera 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 Atomoxetine HCl Aurobindo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 June 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