COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atofab 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules

(atomoxetine hydrochloride)

NL/H/4032/001-007/DC

Date: 8 January 2019

This module reflects the scientific discussion for the approval of Atofab 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules. The procedure was finalised on 14 March 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

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 Atofab 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules, from G.L. Pharma GmbH.

The product 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 Atofab 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 medicinal 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 medicinal product 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 procedure concerns a generic application claiming essential similarity with the innovator products Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (NL License RVG 31494-31498,100389 & 100392) which have been registered in the Netherlands by Eli Lilly Nederland BV since 15 December 2004 through mutual recognition procedure UK/H/0686/001-007/DC.

The concerned member states (CMS) involved in this procedure were
Atofab 10 mg - Austria, Bulgaria, Czech Republic, Romania and Slovak Republic
Atofab 18 mg - Austria, Czech Republic, Romania and Slovak Republic

Atofab 25 mg - Austria, Bulgaria, Czech Republic, Romania and Slovak Republic
Atofab 40 mg - Austria, Bulgaria, Czech Republic, Romania and Slovak Republic
Atofab 60 mg - Austria, Bulgaria, Czech Republic, Romania and Slovak Republic
Atofab 80 mg - Austria
Atofab 100 mg - Austria

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

II. QUALITY ASPECTS

II.1 Introduction

Atofab 10 mg is a hard gelatin capsule with a opaque white cap imprinted in black ink with '10' and a opaque white body imprinted in black ink with 'mg' containing a white powder. Each capsule contains 10 mg atomoxetine as 11.43 mg atomoxetine hydrochloride.

Atofab 18 mg is a hard gelatin capsule with a opaque rich yellow cap imprinted in black ink with '18' and a opaque white body imprinted in black ink with 'mg' containing a white powder. Each capsule contains 18 mg atomoxetine as 20.57 mg atomoxetine hydrochloride.

Atofab 25 mg is a hard gelatin capsule with a opaque blue cap imprinted in black ink with '25' and a opaque white body imprinted in black ink with 'mg' containing a white powder. Each capsule contains 25 mg atomoxetine as 28.57 mg atomoxetine hydrochloride.

Atofab 40 mg is a hard gelatin capsule with a opaque blue cap imprinted in black ink with '40' and a opaque blue body imprinted in black ink with 'mg' containing a white powder. Each capsule contains 40 mg atomoxetine as 45.71 mg atomoxetine hydrochloride.

Atofab 60 mg is a hard gelatin capsule with a opaque blue cap imprinted in black ink with '60' and a opaque rich yellow body imprinted in black ink with 'mg' containing a white powder. Each capsule contains 60 mg atomoxetine as 68.57 mg atomoxetine hydrochloride.

Atofab 80 mg is a hard gelatin capsule with a opaque brown cap imprinted in black ink with '80' and a opaque white body imprinted in black ink with 'mg' containing a white powder. Each capsule contains 80 mg atomoxetine as 91.42 mg atomoxetine hydrochloride.

Atofab 100 mg is a hard gelatin capsule with a opaque brown cap imprinted in black ink with '100' and a opaque brown body imprinted in black ink with 'mg' containing a white powder. Each capsule contains 100 mg atomoxetine as 114.28 mg atomoxetine hydrochloride.

The capsules are packed in transparent PVC/PE/PCTFE-Aluminium foil blisters or PA/AL/PVC-Aluminium foil blisters.

The excipients are:
Capsule content - pregelatinised maize starch, silica colloidal anhydrous and dimeticone (350)
Capsule shell –
Atofab 10 mg: gelatin, sodium lauryl sulfate (E487), titanium dioxide (E171) and purified water
Atofab 18 mg: gelatin, sodium lauryl sulfate (E487), titanium dioxide (E171), iron oxide yellow (E172) and purified water
Atofab 25 mg: gelatin, sodium lauryl sulfate (E487), titanium dioxide (E171), indigo carmine (E132) and purified water
Atofab 40 mg: gelatin, sodium lauryl sulfate (E487), titanium dioxide (E171), indigo carmine (E132) and purified water
Atofab 60 mg: gelatin, sodium lauryl sulfate (E487), titanium dioxide (E171), indigo carmine (E132), iron oxide yellow (E172) and purified water
Atofab 80 mg: gelatin, sodium lauryl sulfate (E487), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172) and purified water
Atofab 100 mg: gelatin, sodium lauryl sulfate (E487), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172)and purified water
Printing ink (black) - shellac glaze-45% (20% esterified) in ethanol, iron oxide black (E172) and propylene glycol

II.2 Drug Substance

The active substance is atomoxetine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder and sparingly soluble in water, soluble in anhydrous ethanol and practically insoluble in heptane. Atomoxetine hydrochloride shows polymorphism; form A is used.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional tests for polymorphic form, residual solvents (as mentioned on the CEP). Absence of a test for microbiological

purity and particle size has been justified. Batch analysis data showing compliance to the specification is provided of two batches. Validation of the analytical procedures has performed. Information on reference standards has been provided.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients has been explained and justified. The suitability of the product for the paediatric population has been discussed. A risk assessment on elemental impurities has been provided.

A bioequivalence study was performed with the test product Atofab 60 mg hard capsules and reference product Strattera 60 mg hard capsules. Biowaivers of strength are requested for the additional strengths 10 mg, 18 mg, 25 mg, 40 mg, 80 mg and 100 mg. Dissolution profiles in suitable media (pH 1.2, 4.5 and 6.8) are provided.

Manufacturing process
The manufacturing process consists of three mixing steps, encapsulation and packaging. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for 3 batches of the 10 mg, 60 mg and 100 mg strengths and 1 batch of the 18 mg, 25 mg, 48 mg and 80 mg strengths in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the applicable specifications. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass and mass uniformity, loss on drying, disintegration, identification, assay, related substances, isomeric purity, dissolution, uniformity of dosage units and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data 3 batches of the 10 mg, 60 mg and 100 mg strengths and 1 batch of the 18 mg, 25 mg, 48 mg and 80 mg strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 batches of the 10 mg, 60 mg and 100 mg strengths and 1 batch of the 18 mg, 25 mg, 48 mg and 80 mg strengths stored at

25°C/60%RH (24 months), 30°C/65%RH (24 months) and 40°C/75%RH (6 months). Several stability commitments covering number of batches per strength, scale and duration of studies have been provided. Stability study results available till now demonstrate compliance with the proposed specification. A shelf-life period of 36 months without a storage precaution can be granted.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies

The excipient gelatin is of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atofab 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 Atofab 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

Atomoxetine 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 conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atofab 60 mg hard capsules (G.L. Pharma GmbH, Austria) is compared with the pharmacokinetic profile of the reference product Strattera 60 mg hard capsules (Eli Lilly Nederland B.V., NL).

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

Biowaiver

The MAH presented as support for the biowaiver the composition of the test products and dissolution data. All strengths of the test product have the same qualitative composition and are quantitatively dose-proportional. The comparative dissolution data between the test biobatch 60 mg and the additional strengths 10, 18, 25, 40, 80 and 100 mg demonstrated similarity at pH 1.2, 4.5 and 6.8 as all dissolved very rapidly, with more than 85% of the drugs dissolved within 15 minutes. Overall, all the criteria for a biowaiver based on the current Guideline on the Investigation of Bioequivalence are met. Hence, a biowaiver for the additional strengths 10, 18, 25, 40, 80 and 100 mg can be granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 72 healthy male and female subjects, aged 18-44 years. Each subject received a single dose (60 mg) of one of the 2 atomoxetine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 13 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 48, 60 and 72 after administration of the products.

The design of the study is acceptable. A single dose study under fasting conditions is considered sufficient to support an application for an immediate-release product with several strengths. The 60 mg strength has been used in the bioequivalence study instead of the highest strength (100 mg). However, considering the linear pharmacokinetics of atomoxetine in the range 10 -100 mg, the use of 60 mg strength is acceptable.

The proposed products can be taken with and without food. Hence, a study in the fasting condition is agreed as this more sensitive to detect differences between the test and reference product in accordance to the Guideline on the Investigation of Bioequivalence.

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
Two subjects did not report to the facility at the second period admission and three subjects reported adverse events in the first or second period and were withdrawn. Therefore, 66 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=66	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	3970 ± 4589	4146 ± 5060	499 ± 165	1.0 (0.5 – 8.0)
Reference	3815 ± 4125	4012 ± 4678	473 ± 153	1.0 (0.5 – 8.0)
***Ratio (90% CI)**	1.01 (0.99 – 1.04)	1.01 (0.99 – 1.04)	1.05 (0.99 – 1.12)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Atofab 60 mg hard capsules is considered bioequivalent with Strattera 60 mg hard capsules.

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).

The results of the bioequivalence study with 60 mg hard capsules formulation can be extrapolated to other strengths 10 mg, 18 mg, 25 mg, 40 mg, 80 mg and 100 mg according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Atofab

- Summary table of safety concerns as approved in RMP

Important identified risks	- Suicidal ideation - Hepatic injury - Increased blood pressure an increased heart rate - Peripheral vascular instability (Raynaud's phenomenon)
Important potential risks	- Cardiovascular and cerebrovascular outcomes: • myocardial ischaemia • tachyarrhythmia • cerebrovascular accident • QTc prolongation - Aggression/hostility - Seizure
Missing information	None

The MAH is obliged to ensure distribution of the educational material prior to launching the medicinal product onto the market. Distribution methods should be agreed with the national competent authorities.
The aim of the educational material, is to reinforce the label recommendations regarding medical history, and comorbidities assessments at baseline for contraindications and values to be monitored, and provide support for monitoring heart rate and blood pressure.

The educational material should contain the following key elements:

- Physician's guide for assessing and monitoring cardiovascular risk when prescribing atomoxetine
- A checklist for actions to take before prescribing /dispensing or administering atomoxetine
- A checklist for actions to take during monitoring to manage cardiovascular risks with atomoxetine treatment and measurement recording chart.
- Measurement recording chart (to help keep good records of blood pressure and heart rate during atomoxetine treatment

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator 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 Strattera (UK/H/686/002-008/II/50). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atofab 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms 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 Atofab with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 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