Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Atomoxetine 10mg Hard Capsules
Atomoxetine 18mg Hard Capsules
Atomoxetine 25mg Hard Capsules
Atomoxetine 40mg Hard Capsules
Atomoxetine 60mg Hard Capsules
Atomoxetine 80mg Hard Capsules
Atomoxetine 100mg Hard Capsules

(Atomoxetine hydrochloride)

Procedure No: UK/H/6038/001-007/DC

UK Licence Number: PL 24668/0303-0309

Caduceus Pharma Ltd.

LAY SUMMARY

Atomoxetine 10mg, 18mg, 25mg, 40mg, 60mg, 80mg and 100mg Hard Capsules
(atomoxetine hydrochloride, hard capsule, 10mg, 18mg, 25mg, 40mg, 60mg, 80mg and 100mg)

This is a summary of the Public Assessment Report (PAR) for Atomoxetine 10mg, 18mg, 25mg, 40mg, 60mg, 80mg and 100mg Hard Capsules (PL 24668/0303-0309; UK/H/6038/001-007/DC). It explains how Atomoxetine 10mg, 18mg, 25mg, 40mg, 60mg, 80mg and 100mg Hard Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Atomoxetine 10mg, 18mg, 25mg, 40mg, 60mg, 80mg and 100mg Hard Capsules.

The products will be collectively referred to as Atomoxetine Capsules throughout the remainder of this public assessment report (PAR).

For practical information about using Atomoxetine Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Atomoxetine Capsules and what are they used for?
Atomoxetine Capsules are 'generic medicines'. This means that Atomoxetine Capsules are similar to 'reference medicines' already authorised in the European Union (EU) called Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (Eli Lilly and Company Limited, UK).

Atomoxetine Capsules contain atomoxetine and are used to treat attention-deficit and hyperactivity disorder (ADHD). They are used:

- in children over six years of age
- in young people
- in adults

This medicine is used only as a part of the total treatment of the disease which also requires treatments that do not involve medicines, such as counselling and behavioural therapy.

This medicine is not for use as a treatment for ADHD in children under 6 years of age as it is not known if the drug works or is safe in this age group.

In adults, Atomoxetine Capsules are used to treat ADHD when the symptoms are very troublesome and affect the patient's work or social life and when they have had symptoms of the disease as a child.

How do Atomoxetine Capsules work?
This medicine contains the active ingredient atomoxetine hydrochloride which works by increasing the amount of noradrenaline in the brain. This is a chemical that is produced naturally, and increases attention and decreases impulsiveness and hyperactivity in patients with ADHD. The medicine is prescribed to help control the symptoms of ADHD. This medicine is not a stimulant and is therefore not addictive.

It may take a few weeks after the patient starts the medicine for their symptoms to fully improve.

About ADHD
Children and young people with ADHD find it:

- hard to sit still and
- hard to concentrate.

It is not their fault that they cannot do these things. Many children and young people struggle to do these things. However, with ADHD this can cause problems with everyday life. Children and young people

with ADHD may have difficulty learning and doing homework. They find it hard to behave well at home, at school or in other places. ADHD does not affect the intelligence of a child or young person.

Adults with ADHD find it difficult to do all the things that children find difficult; however this may mean they have problems with:

- work
- relationships
- low self esteem
- education.

How are Atomoxetine Capsules used?
The pharmaceutical form of this medicine is a hard capsule and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure. This is usually one or two times a day (morning and late afternoon or early evening).

- Children should not take this medicine without help from an adult
- If the patient is taking Atomoxetine Capsules once a day and experiences sleepiness or feel sick, their doctor may change their treatment schedule to twice a day
- The capsules should be swallowed whole, either with or without food
- The capsules should not be opened and the contents inside the capsules should not be removed and taken in any other way
- Taking the medicine at the same time each day may help the patient to remember to take it.

Use in children and adolescents
If the patient is a child or teenager (6 years or older):
The patient's doctor will tell them how much Atomoxetine Capsules they should take and will calculate this according to their weight. He/she will normally start the patient on a lower dose before increasing the amount of Atomoxetine Capsules they need to take according to their body weight.

- Body weight up to 70kg: a starting total daily dose of 0.5mg per kg of body weight for a minimum of 7 days. The patient's doctor may then decide to increase this to the usual maintenance dose of about 1.2mg per kg of body weight daily.
- Body weight over 70kg: a starting total daily dose of 40mg for a minimum of 7 days. The patient's doctor may then decide to increase this to the usual maintenance dose of 80mg daily. The maximum daily dose their doctor will prescribe is 100mg.

Adults

- Atomoxetine Capsules should be started at a total daily dose of 40mg for a minimum of 7 days. The patient's doctor may then decide to increase this to the usual maintenance dose of 80-100mg daily. The maximum daily dose their doctor will prescribe is 100mg.

If the patient has problems with their liver, the patient's doctor may prescribe a lower dose.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Atomoxetine Capsules have been shown in studies?
Because Atomoxetine Capsules are generic medicines, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (Eli Lilly and Company Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Atomoxetine Capsules?
Because Atomoxetine Capsules are generic medicines and bioequivalent to the reference medicine Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (Eli Lilly and Company Limited, UK), its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Atomoxetine Capsules, see section 4 of the package leaflet available on the MHRA website.

Why was Atomoxetine Capsules approved?
It was concluded that, in accordance with EU requirements, Atomoxetine Capsules have been shown to have comparable quality and to be bioequivalent to Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (Eli Lilly and Company Limited, UK). Therefore, the MHRA decided that, as for Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (Eli Lilly and Company Limited, UK); the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Atomoxetine Capsules?
A risk management plan (RMP) has been developed to ensure that Atomoxetine Capsules is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Atomoxetine Capsules including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Atomoxetine Capsules
The marketing authorisations for Atomoxetine Capsules were granted in the UK on 10 March 2016.

The full PAR for Atomoxetine Capsules follows this summary.

For more information about use of Atomoxetine Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2016.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Caduceus Pharma Ltd, marketing authorisations for the medicinal products Atomoxetine Capsules (PL 24668/0303-0309; UK/H/6038/001-007/DC). The products are prescription-only medicines (POM) 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 Capsules 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.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Luxembourg as Concerned Member State (CMS). The applicant subsequently withdrew the applications in Luxembourg during the procedure, leaving no CMS. The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg hard capsules (PL 0006/0375-0379) which were authorised to Eli Lilly and Company Limited, UK on 27 May 2004 and Strattera 80 mg and 100 mg hard capsules (PL 0006/0615-0616), which were authorised to Eli Lilly and Company Limited, UK on 05 June 2008.

Atomoxetine (pharmacotherapeutic group: psychoanaleptics, centrally acting sympathomimetics, ATC code: N06BA09) is a highly selective and potent inhibitor of the pre synaptic noradrenaline transporter, its presumed mechanism of action, without directly affecting the serotonin or dopamine transporters. Atomoxetine has minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Atomoxetine has two major oxidative metabolites: 4 hydroxyatomoxetine and N desmethylatomoxetine. 4 Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the noradrenaline transporter but unlike atomoxetine, this metabolite also exerts some inhibitory activity at the serotonin transporter. However, any effect on this transporter is likely to be minimal, as the majority of 4 hydroxyatomoxetine is further metabolised such that it circulates in plasma at much lower concentrations (1% of atomoxetine concentration in extensive metabolisers and 0.1% of atomoxetine concentration in poor metabolisers). N Desmethylatomoxetine has substantially less pharmacological activity compared with atomoxetine. It circulates in plasma at lower concentrations in extensive metabolisers and at comparable concentrations to the parent drug in poor metabolisers at steady state.

Atomoxetine is not a psychostimulant and is not an amphetamine derivative. In a randomised, double-blind, placebo-controlled, abuse-potential study in adults comparing effects of atomoxetine and placebo, atomoxetine was not associated with a pattern of response that suggested stimulant or euphoriant properties.

Two bioequivalence studies (conducted under fasting conditions) were submitted to support these applications, comparing the applicant's test products Atomoxetine 40mg and 60mg Hard Capsules (Caduceus Pharma Ltd) with the reference products Strattera 40 mg and 60 mg hard capsules (Eli Lilly and Company Limited, UK). The applicant has stated that the bioequivalence studies were conducted in compliance with the Declaration of Helsinki and in compliance with the International Conference on Harmonisation Good Clinical Practice (GCP) guidelines (1996), and European Guidelines.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

II QUALITY ASPECTS

II.1 Introduction

Each hard capsule contains atomoxetine hydrochloride equivalent to 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg or 100 mg of atomoxetine, as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

All strengths:
Capsule shell
Gelatin and titanium dioxide (E171).

The 18 mg capsule strength also contains yellow iron oxide (E172).
The 25 mg capsule strength also contains FD&C Blue 2 (E132) and black iron oxide (E172).
The 40 mg capsule strength also contains indigotine – FD&C Blue 2 (E132) and black iron oxide (E172).
The 60 mg capsule strength also contains indigotine – FD&C Blue 2 (E132), black iron oxide (E172) and yellow iron oxide (E172).
The 80 mg and 100 mg capsule strengths also contain yellow iron oxide (E172) and red iron oxide (E172).

All strengths:
Capsule Content:
Co-processed corn starch consisting of corn starch and pregelatinised corn starch (Starcap 1500), Dimethicone 350 cs and sodium starch glycolate.

All strengths:
Printing ink:
Shellac, propylene glycol, ammonia solution, black iron oxide (E172) and potassium hydroxide

All strengths of the finished product are packed into opaque polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC)/PVC/aluminium blisters and are available in pack sizes of

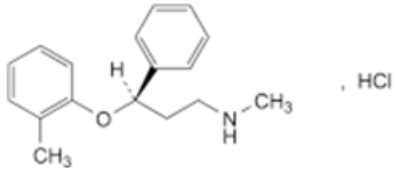
- 10 mg 18 mg, 25 mg and 40 mg strengths: 7 and 28 hard capsules.
- 60 mg, 80 mg and 100 mg strengths: 28 hard capsules.

Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Atomoxetine hydrochloride
Chemical name: (3*R*)-N-Methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine hydrochloride.

Structure:



Molecular formula: $C_{17}H_{22}ClNO$
Molecular weight: 291.8
Description: White or almost white powder.
Solubility; Sparingly soluble in water, soluble in anhydrous ethanol, practically insoluble in heptane.

Atomoxetine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, atomoxetine hydrochloride, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious hard capsules containing 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg or 100 mg of atomoxetine per capsule, that are generic versions of the reference products Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (Eli Lilly and Company Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Starcap 1500 and the empty capsule shells which are in compliance with suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation studies on future commercial-scale batches.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg strengths of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of atomoxetine hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Atomoxetine Capsules are 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.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of atomoxetine hydrochloride is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of atomoxetine hydrochloride.

Based on the data provided, Atomoxetine Capsules can be considered bioequivalent to Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules (Eli Lilly and Company Limited, UK).

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence studies:

STUDY 1

An open-label, balanced, randomised, single oral dose, three-treatment, three-sequence, three-period, three-way crossover bioequivalence study of the applicant's test product Atomoxetine 60mg Hard Capsules (Caduceus Pharma Ltd) versus the reference product Strattera 60 mg hard capsules (Eli Lilly and Company Limited, UK) in healthy, adult, subjects under fasting conditions.

The three -way design was chosen in order to include a second reference product from the Australian market. This is acceptable.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 60 mg hard capsule) of the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 8 days. The pharmacokinetic results are presented below:

Table: Summary of pharmacokinetic parameters for atomoxetine:

	Test	Reference
AUC_{0-t} [ng.h/ml]	2748.42 (73.24)	2733.49 (67.40)
AUC_{0-inf} [ng.h/ml]	2794.36 (73.66)	2778.44 (68.11)
C_{max} [ng/ml]	465.71 (34.84)	500.57 (23.41)
t_{max} [h]	1.72 (79.82)	1.13 (71.44)
AUC ratio [%]	98.41 (0.73)	98.48 (0.72)

AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration

Table: Bioequivalence of Test and Reference products:

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio (%)	98.51	98.58	90.61
90% geometric C.I.	93.86 - 103.39	93.96 - 103.43	81.56 - 100.67
Intra-subject CV (%)	8.78	8.72	19.26

STUDY 2
An open-label, balanced, randomised, single oral dose, three-treatment, three-sequence, three-period, three-way crossover bioequivalence study of the applicant's test product Atomoxetine 40mg Hard Capsules (Caduceus Pharma Ltd) versus the reference product Strattera 40 mg hard capsules (Eli Lilly and Company Limited, UK) in healthy, adult, subjects under fasting conditions.

The three -way design was chosen in order to include a second reference product from the Australian market. This is acceptable.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 40 mg hard capsule) of the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 8 days. The pharmacokinetic results are presented below:

Table: Summary of pharmacokinetic parameters for atomoxetine:

Pharmacokinetic parameter	Geometric mean		Arithmetic mean		Standard deviation	
	B	C	B	C	B	C
AUC_{0-t} (ng.h/mL)	1392.32	1365.60	1587.37	1545.65	1124.699	970.979
C_{max} (ng/mL)	282.40	274.25	297.24	284.76	101.173	78.190

Atomoxetine (Test Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
AUC_{0-t} (ng.h/mL)	1444.66	1641.44	1091.592
C_{max} (ng/mL)	289.54	303.07	95.136

AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
B=EU reference product Strattera 40 mg hard capsules (Eli Lilly and Company Limited, UK).
C=Australian reference product

Table: Ratio and 90% Confidence Intervals of test product versus Reference Product:

Test A Vs. Reference B

Pharmacokinetic parameter	Ratio (%)	90% Confidence Intervals		Intra Subject Variability (%)
		Lower 90% CI (%)	Upper 90% CI (%)	
AUC_{0-t}	103.42	99.33	107.67	7.92
C_{max}	102.30	94.14	111.16	16.42

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for atomoxetine for the 40 mg and 60 mg test product strengths lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test products Atomoxetine 40mg and 60 mg Hard Capsules (Caduceus Pharma Ltd) are bioequivalent to the reference products Strattera 40 mg and 60 mg hard capsules (Eli Lilly and Company Limited, UK).

As the 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence studies with the 40 mg and 60 mg capsule strengths can be extrapolated to the 10 mg, 18 mg, 25 mg, 80 mg and 100 mg strength capsules.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety

No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Capsules.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	Suicidal ideation
	Hepatic injury
	Increased blood pressure and increased heart rate
	Peripheral vascular instability (Raynaud's phenomenon)
Important potential risks	Cardiovascular and cerebrovascular outcomes • QTc prolongation • Myocardial ischaemia • Tachyarrhythmia • Cerebrovascular accident
	Aggression/hostility
	Seizures
Missing information	No important missing information has been identified

Summary table of risk minimisation measures:

Important identified risks		
Safety concern	**Summary of Routine Risk Minimisation Activities**	**Summary of Additional Risk Minimisation Activities**
Suicidal ideation	Routine risk minimisation measures are sufficient for this safety concern as information is included in Sections 4.4 and 4.8 of the SmPC.	N/A
Hepatic injury	Routine risk minimisation measures are sufficient for this safety concern as information is included in Sections 4.4 and 4.8 of the SmPC.	N/A
Increased blood pressure and increased heart rate	Routine risk minimisation through appropriate wording in the SmPC included in Sections 4.2, 4.3, 4.4, 4.5, 4.8 and 4.9.	Distribution of a Direct Healthcare Professional Communication (DHPC) (see Annex 10) Prescriber Pack will include: - Introductory Cover Letter - A copy of the SmPC - Physician's Guide including additional tools: • Checklist for actions to take before prescribing/dispensing or administering of atomoxetine • Checklist for monitoring to manage cardiovascular risks with atomoxetine treatment • Measurements recording chart
Peripheral vascular instability (Raynaud's phenomenon)	Routine risk minimisation measures are sufficient for this safety concern as information is included in Section 4.8.	N/A

Important potential risks		
Safety concern	**Summary of Routine Risk Minimisation Activities**	**Summary of Additional Risk Minimisation Activities**
Cardiovascular and cerebrovascular outcomes (QTc prolongation, myocardial ischaemia, tachyarrhythmia and cerebrovascular accident)	Routine risk minimisation measures are sufficient for this safety concern as information is included in Sections 4.3, 4.4, 4.5, 4.8 and 4.9 of the SmPC.	N/A
Aggression/hostility	Routine risk minimisation measures are sufficient for this safety concern as information is included in Sections 4.4 and 4.8 of the SmPC.	N/A

Seizures	Routine risk minimisation measures are sufficient for this safety concern as information is included in Sections 4.4, 4.5, 4.8 and 4.9 of the SmPC.	N/A

IV.7 Discussion on the clinical aspects

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant's test products Atomoxetine 40mg and 60 mg Hard Capsules (Caduceus Pharma Ltd) and the reference products Strattera 40 mg and 60 mg hard capsules (Eli Lilly and Company Limited, UK).

As the 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence studies with the 40 mg and 60 mg capsule strengths can be extrapolated to the 10 mg, 18 mg, 25 mg, 80 mg and 100 mg strength capsules.

The grant of marketing authorisations is recommended for these applications.

V User consultation

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 language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI Overall conclusion, benefit/risk assessment and recommendation

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

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for this medicine. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 10mg Hard Capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains atomoxetine hydrochloride equivalent to 10mg of atomoxetine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

7 capsules
28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Caduceus Pharma Ltd.
6th floor
94 Wigmore Street
London
W1U 3RF
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0303

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

atomoxetine 10mg hard capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 10mg Hard Capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 18mg Hard Capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains atomoxetine hydrochloride equivalent to 18mg of atomoxetine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

7 capsules
28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Caduceus Pharma Ltd.
6th floor
94 Wigmore Street
London
W1U 3RF
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0304

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

atomoxetine 18mg hard capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 18mg Hard Capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 25mg Hard Capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains atomoxetine hydrochloride equivalent to 25mg of atomoxetine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

7 capsules
28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Caduceus Pharma Ltd.
6th floor
94 Wigmore Street
London
W1U 3RF
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0305

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

atomoxetine 25mg hard capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 25mg Hard Capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 40mg Hard Capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains atomoxetine hydrochloride equivalent to 40mg of atomoxetine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

7 capsules
28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Caduceus Pharma Ltd.
6th floor
94 Wigmore Street
London
W1U 3RF
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0306

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

atomoxetine 40mg hard capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 40mg Hard Capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 60mg Hard Capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains atomoxetine hydrochloride equivalent to 60mg of atomoxetine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Caduceus Pharma Ltd.
6th floor
94 Wigmore Street
London
W1U 3RF
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0307

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

atomoxetine 60mg hard capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 60mg Hard Capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 80mg Hard Capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains atomoxetine hydrochloride equivalent to 80mg of atomoxetine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Caduceus Pharma Ltd.
6th floor
94 Wigmore Street
London
W1U 3RF
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0308

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

atomoxetine 80mg hard capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 80mg Hard Capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 100mg Hard Capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains atomoxetine hydrochloride equivalent to 100mg of atomoxetine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Caduceus Pharma Ltd.
6th floor
94 Wigmore Street
London
W1U 3RF
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0309

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

atomoxetine 100mg hard capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Atomoxetine 100mg Hard Capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER