MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

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10 May 2022

s 9(2)(a)

By email: s 9(2)(a)
Ref: H202204053

Dear s 9(2)(a)

Response to your request for official information

Thank you for your request under the Official Information Act 1982 (the Act) on 16 March 2022 for information relating to the approving of medications, specifically Atomoxetine. You stated:

> *I have been reading through the Medsafe website to learn more about generic medications. More specifically, the processes that Medsafe goes through before approving a generic mediation as well as the quality and safety monitoring process and testing that occurs following the approval of a generic medication.*
>
> *I'm finding the website a little bit confusing to navigate so if it is possible, could you please provide me some information on the following topics;*
>
> *By the way, I completely understand that a generic medication has to contain the same active ingredient as the original brand name and that it can contain different excipients/fillers/bulking agents.*
>
> *My requests are regarding both forms of generic Atomoxetine available in New Zealand and specifically, regarding the 100mg capsules.*
> *I will refer to both of these forms of Atomoxetine as "Atomoxetine 100mg capsules".*

Before responding to your specific request, I would like to provide some background to Medsafe's processes for the regulation of medicines. Medsafe thoroughly assesses applications for the approval of new generic medicines to ensure they meet international standards of quality, safety and efficacy, including that they are demonstrated to be bioequivalent to the relevant innovative medicine, before they can be supplied in New Zealand. More information regarding the regulation of generic medicines in New Zealand can be found on the Medsafe website at:

- www.medsafe.govt.nz/profs/PUArticles/Mar2013GenericMedBioqueivalence.htm.
- www.medsafe.govt.nz/profs/PUArticles/September2017/TheMedsafeFiles4NMAssessment.htm.
- www.medsafe.govt.nz/publications/media/2019/Q&AonGenericMedicines%20.asp.

Please find a response to each part of your request below.

1. *A copy of the application/s to sell "Atomoxetine 100mg capsules" in NZ, including the information demonstrating that the quality of the medicine meets acceptable standards and functions as well as the respective innovator.*

While Medsafe has considered your request, it has been determined that releasing the entirety of the application dossier would require substantial collation. This is considered 'substantial' as it would have a significant and unreasonable impact Medsafe and its ability to carry out its critical operations. Therefore, this request is refused under section 18(f) of the Act.

However, even if the request was refined to a manageable scope much of the information contained in the dossier is likely to be withheld under section 9(2)(b)(ii) of the Act, where its release would likely unreasonably prejudice the commercial position of the person who supplied the information.

To provide reasonable assistance under section 13 of the Act, information on approved generic atomoxetine medicines is also publicly available and can be found at: https://www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=16245 and https://www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=18246. You may also be interested in information about the Medsafe approval process for medicines available at: www.medsafe.govt.nz/Medicines/regulatory-approval-process.asp.

2. *A copy of the result/s of the testing used to ensure all the ingredients of "Atomoxetine 100mg capsules" meet the required standards for purity and concentration.*

Please see attached copies of certificates of analysis for Atomoxetine (Arrotex) 100 mg capsules and Apo-Atomoxetine 100 mg capsules. These certificates detail the results of quality control release testing of one batch of finished product for each medicine against the approved specifications. Some information within the certificates of analysis is withheld under:

- section 9(2)(a) to protect the privacy of natural persons; and
- section 9(2)(b)(ii) where its release would likely unreasonably prejudice the commercial position of the person who supplied the information.

3. *A copy of the latest report from the certified inspectors who verify that manufacturing and testing are conducted by "Good Manufacturing Practice".*

Medsafe does not hold the Good Manufacturing Practice (GMP) audit reports. Evidence of compliance with GMP for all manufacturing, testing and packing sites is provided with a new medicine application, which is typically in the form of a GMP certificate. GMP audit reports are not required to be provided as Medsafe recognises the GMP certificates issued by certain recognised overseas regulatory authorities. The requirements for suppling evidence of GMP can be found in our guidelines at: www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/manufacture-of-medicines.pdf.

4. *Proof/verification of the credentials of the certified inspectors mentioned in paragraph 3.*

This part of your request is refused under section 18(e) of the Act, on the basis that the information requested not exist. However, please refer to question 3 regarding requirements for providing evidence of current GMP.

5. *The full results of the bioequivalence study/studies for "Atomoxetine 100mg capsules".*

Please see attached a copy of the bioequivalence study synopsis for Apo-Atomoxetine. Some information in the bioequivalence study synopsis for Apo-Atomoxetine is withheld under section 9(2)(a) and section 9(2)(b)(ii) of the Act.

However, this information does not exist for Atomoxetine (Arrotex) as a BCS-based biowaiver was granted in lieu an in vivo bioequivalence study. You may be interested in the following links to international guidance regarding bioequivalence and BCS-based biowaivers.

International Council for Harmonisation (ICH) M9: Biopharmaceutics classification system-based biowaivers guideline:
https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf.
European Medicines Agency (EMA) guideline on the investigation of bioequivalence:
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf.

6. *A copy of all of the results of the routine testing conducted by ESR relating to "Atomoxetine 100mg capsules" if applicable.*

This part of your request is refused under section 18(e) of the Act, on the basis that the information requested does not exist. Medsafe has a medicines testing program which includes routine testing of medicines which have been approved for distribution in New Zealand. Medicines are selected for routine testing to cover a range of products, dose forms, manufacturers, and sponsors. In addition, the testing program includes testing of some medicines for which there has been a quality complaint or where there is a suspected quality issue. Atomoxetine has not been selected for testing under the program.

7. *A copy of all of the formal notifications from other regulators/suppliers in NZ about inspection findings relating to "Atomoxetine 100mg capsules"*

This part of your request is refused under section 18(e) of the Act, on the basis that the information requested not exist for these medicines. Medsafe monitors alerts from international communities and regulatory authorities, for example the US Food and Drug Administration warning letters and international rapid alerts. In addition, sponsors of medicines are responsible for ensuring Medsafe is notified of any such issues.

8. *If possible, the latest gas chromatography-mass spectrometry report for "Atomoxetine 100mg capsules".*

This part of your request is refused under section 18(e) of the Act, on the basis that the information requested does not exist as these products are not tested using gas chromatography-mass spectrometry. See the response to question 2 regarding other testing results.

Under section 28(3) of the Act, you have the right to ask the Ombudsman to review any decisions made under this request. The Ombudsman may be contacted by email at: info@ombudsman.parliament.nz or by calling 0800 802 602.

Yours sincerely

Chris James
Group Manager
Medsafe

s 9(2)(b)(ii) [redacted]

s 9(2)(b)(ii) [redacted]

CERTIFICATE OF ANALYSIS № 412 112069

Product: ATOMOXETINE CAPSULE 100 mg GENERIC PARTNERS /NZ/
Index: ATMK-1691-800

Lot No		[redacted]
Manufacturing date		**01.2020**
Expiry date		**01.2023**
Lot size		**819 x 28**
T E S T	**REQUIREMENTS**	**RESULTS**
Appearance of capsules	s 9(2)(b)(ii) [redacted]	conforms
Appearance of content		conforms
Capsules average net weight		283.4 mg
Uniformity of dosage units - mass variation		9.7 %
Identification of atomoxetine - liquid chromatography (HPLC with UV diode array detector)		conforms conforms
Identification of titanium dioxide [N1] **- chemical identification**		conforms
Identification of iron oxide [N1] **- chemical identification**		conforms
Water content in capsule filling		3.9 %
Related substances by HPLC - single unknown impurities - total impurities		less than 0.1 % less than 0.1 %
Assay of atomoxetine in 1 capsule		98.3 %
Assay of (S)-enantiomer (HPLC)		less than 0.05 %
Dissolution test of atomoxetine from capsule after 30 min.		105.4 % (min.101.3% max.110.3%)
Microbiological tests[N2] **Total aerobic microbial count (TAMC) in 1 g** **Total yeasts/moulds count (TYMC) in 1 g** **Escherichia coli in 1 g**		conforms

[N1] Non-routine test. Testing frequency – every 10th batch but at least once a year.
[N2] Routine test for first 10 commercial batches, then non-routine test (testing frequency – every 10th batch) but not rarely than one batch a year.

CONCLUSION: This material complies with the requirements of the [redacted]

Prepared by: s 9(2)(a) [redacted]
Reviewed by: s 9(2)(a) [redacted]
Approved by: s 9(2)(a) [redacted]

Date: 24.02.2021

The English version is only a true copy of the Polish CoA, and the real analysis date corresponds to the one on the Polish certificate

s 9(2)(b)(ii) [redacted]

APOTEX
Innovating for patient affordability

s 9(2)(a) [redacted]

Version: 1
Effective date: 04-Jul-2017

Approved By: s 9(2)(a) [redacted]
Date: 6/29/2017 3:43:51PM

s 9(2)(a) [redacted]

Approved By: s 9(2)(a) [redacted]
Date: 7/4/2017 8:27:08PM

Specification and Certificate of Analysis

Material: ATOMOXETINE HCL CAP USP 100 MG APO
Material #: s 9(2)(b)(ii) [redacted]
Batch No.:
Storage Precautions: Store in a tight container at controlled room temperature (15-30°C)
Date Manufactured: 02/07/2018
Testing Site: Apotex Inc., 50 Steinway Blvd., Etobicoke, ON, Canada

TEST	SPECIFICATION		RESULTS
	METHOD	ACCEPTANCE CRITERIA	
APPEARANCE	s 9(2)(b)(ii) [redacted]		Conforms
IDENTIFICATION			Conforms
IDENTIFICATION			Conforms
AVERAGE WEIGHT			449mg
DISSOLUTION			Mean: 96% % RSD: 1.7% Minimum: 94% Maximum: 98% PASS STAGE1

UNIFORMITY OF DOSAGE UNITS	s 9(2)(b)(ii)	Mean: 100.4% % RSD: 1.7% Minimum: 97.2% Maximum: 102.8% AV: 4.1 PASS STAGE1
DEGRADATION PRODUCTS		BRT BRT BRT BRT
ASSAY		98.8%
RESIDUAL SOLVENTS		Complies
MICROBIAL LIMITS		LT 500 cfu/g LT 100 cfu/g
MICROBIAL LIMITS		Absent

Legend:

Note: Atomoxetine N-amide is controlled as an unknown impurity by ATOM-IMCP-20-SG.

For Microbial Limits tests (methods M-3 & M-6)-Reduced testing frequency of 1 in 10 batches or at least once annually.

* Cumulative calculation based on the residual solvents levels in the ingredients used to produce the drug product.

BRT: Below Reporting Threshold

ND: None Detected

Reporting Threshold: 0.1%

ATM RC1: (R)-N-Methyl-3-phenyl-3-hydroxy-propylamine (Synthetic Impurity and Degradation Product)

ATM RC3: (R)-3-Phenyl-3-(2-methylphenoxy)-propylamine (Synthetic Impurity and Degradation Product)

Approved By: s 9(2)(a) [redacted]

Date: 06-Mar-2018 8:09 pm

1 TITLE PAGE

STUDY TITLE:	A Relative Bioavailability Study Of Atomoxetine HCL 80 mg Capsules Versus Strattera (Atomoxetine HCL) 80 mg Capsules Under Fasted Conditions
TEST DRUG / INVESTIGATIONAL PRODUCT:	Atomoxetine HCl 80 mg Capsules
INDICATION STUDIED:	Not applicable
STUDY DESIGN:	Randomized, single-dose, two-way, open-label, crossover study under fasted conditions
PROTOCOL NO.:	s 9(2)(b)(ii)
PHASE OF DEVELOPMENT:	I
STUDY INITIATION DATE:	25 November 2011 (date of subject check-in)
STUDY COMPLETION DATE:	13 December 2011 (date of last pharmacokinetic blood sample collection)
PRINCIPAL INVESTIGATOR:	s 9(2)(a)
SPONSOR REPRESENTATIVE:	
GOOD CLINICAL PRACTICE STATEMENT:	The study described in this report was performed in accordance with all applicable Good Clinical Practice guidelines, including archiving of essential documents (ICH E6 [R1], June 1996)
REPORT ISSUED:	26 March 2012
VERSION:	Final Version 1.0

2 SYNOPSIS

Name of Sponsor / Company: Apotex Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Atomoxetine HCl 80 mg Capsules		
Name of Active Ingredient: Atomoxetine HCl	Volume: Page:	

Title of Study:
A Relative Bioavailability Study of Atomoxetine HCl 80 mg Capsules Versus Strattera (Atomoxetine HCl) 80 mg Capsules Under Fasted Conditions

Investigators:	
Principal Investigator:	s 9(2)(a)
Sub-Investigators:	
Study Center(s):	s 9(2)(b)(ii)
Publication(s):	None

Study Periods: **Period I:** 26 November 2011 – 29 November 2011 **Period II:** 10 December 2011 – 13 December 2011	**Phase of Development:** Phase I

Date of First Enrollment (study check-in): 25 November 2011

Date of Last Completed (date of last pharmacokinetic blood sample collection): 13 December 2011

Objectives: This study assessed the relative bioavailability of Atomoxetine HCl 80 mg Capsules compared to that of Strattera 80 mg Capsules following a single oral dose (1 x 80 mg capsule) in healthy adult subjects when administered under fasted conditions.

Methodology: This was an open-label, single-dose, randomized, two-period, two-treatment crossover study under fasted conditions. The total duration of the study, screening through study exit, was approximately 7 weeks with a 14-day washout period between doses. At study check-in, the subjects reported to the clinical site at least 10 hours prior to Day 1 dosing and were required to stay for 24 hours after Day 1 dosing. Subjects returned to the clinic for blood collections at 36, 48, and 72 hours post-dose each period.

Number of Subjects (Planned and Analyzed): With an intra-subject coefficient of variability of 24% and a fixed type-I error of 5%, a total sample size of 27 subjects was expected to attain at least 80% statistical power to detect a difference between the Test and Reference treatments, assuming the difference was within 5%. An additional 5 subjects were enrolled to account for potential drop-outs. Therefore a total of 32 subjects were enrolled in the study. Subjects were selected from non-institutionalized subjects consisting of members of the community at large. Plasma concentration data from a total of 30 subjects were included in the statistical analysis.

Main Criteria for Inclusion: Healthy male or female, 18 years of age or older at the time of dosing, with a body mass index (BMI) between 18 – 30 kg/m^2, inclusive, and weight of at least 110 lbs, who were demonstrated to be generally healthy by medical history, physical examinations, vital sign

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Name of Active Ingredient: Atomoxetine HCl	Volume: Page:	

assessments, 12-lead ECGs, clinical laboratory assessments, and by general observations.

Test Product: Atomoxetine HCl 80 mg Capsules

Dose:	1 × 80 mg
Mode of Administration:	Oral
Lot Number:	s 9(2)(b)(ii)

Reference Product: Strattera 80 mg Capsules

Dose:	1 × 80 mg
Mode of Administration:	Oral
Batch Number:	s 9(2)(b)(ii)

Duration of Treatment: The subjects received 1 Atomoxetine HCl 80 mg Capsule and 1 Strattera 80 mg Capsule over a 3-week period with a 14-day washout period between dosing periods. Total study participation, exclusive of screening, was 19 days.

Criteria for Evaluation:

Bioequivalence: The primary pharmacokinetic parameters C_{max} and AUC_{0-t} were transformed to their natural logarithms. For the test formulation, Apotex Inc.'s Atomoxetine HCl 80 mg Capsules to meet bioequivalence criteria when compared to the reference formulation, Strattera 80 mg Capsules, the ratios of means and their 90% confidence intervals for atomoxetine were to be within 80.00 to 125.00% for AUC_{0-t} and C_{max} under fasted conditions.

Safety: All subjects were monitored throughout the confinement portions of the study. Seated blood pressure, pulse, and temperature were measured at screening. Seated blood pressure and pulse were measured within 120 minutes prior to administration of study product to the first study participant (Hour 0 only) and at approximately 12 and 24 hours (± 60 minutes) after each dose. Blood pressure and heart rate were measured at study exit or early termination. Volunteers were queried for problems prior to dosing (*i.e.* conditions which would not have prevented them from study participation, but could have potentially been exacerbated by the test or reference products) at screening and check-in. Subjects were queried for adverse events (AEs) at least every 12 hours throughout the post-dose confinement period, prior to being released from confinement, and at each return visit for the study. All subjects underwent clinical laboratory testing at screening, including hematology, serum chemistry, urine drug screen, and all females were tested for pregnancy. All subjects were asked "Over the past 2 weeks have you felt down, depressed, or hopeless?" and "Over the past 2 weeks have you felt little interest or pleasure in doing things?" Breath alcohol tests, urine drug screens, and pregnancy tests were performed at check-in for each period. At each check-in subsequent to Period I, a blood sample was collected for safety AST (SGOT) & ALT (SGPT) measurements. (Additionally, physical examinations and ECGs were performed at screening and at study exit)

Statistical Methods: The analytical data were used to calculate the following pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} C_{max}, T_{max}, Kel, and $T_{1/2}$. An analysis of variance was used to evaluate the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, C_{max} for differences due to treatments, period, dosing sequence, and subjects within sequence

Name of Sponsor / Company: Apotex Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Atomoxetine HCl 80 mg Capsules		
Name of Active Ingredient: Atomoxetine HCl	Volume: Page:	

Summary & Conclusions:

Pharmacokinetic Results:

For atomoxetine, the pharmacokinetic and statistical results of this study indicate that the test/reference ratio of geometric means for ln-transformed AUC_{0-t} was 96.73% (90% CI 89.88%-104.10%) and C_{max} was 100.62% (90% CI 93.78%-107.96%). The point estimates and their 90% CIs were all contained within the Therapeutic Goods Administration (TGA) -defined acceptance range of 80.00% to 125.00%.

The following table summarizes the geometric means, least squares means (LSM), ratios of means, and 90% confidence intervals of ln-transformed atomoxetine data for Test Product A versus Reference Product B.

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Test Product A vs. Reference Product B
Least Squares Means, Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)
Ln-Transformed data
Atomoxetine
N = s 9(2)(b)(ii)

Parameter	Least Squares Means		Geometric Means*		% Ratio	90% CI (Lower Limit, Upper Limit)
	Atomoxetine HCl 80 mg Capsules	Strattera 80 mg Capsules	Atomoxetine HCl 80 mg Capsules	Strattera 80 mg Capsules		
AUC_{0-t} (ng-hr/mL)	8.246	8.279	3812.00	3940.91	96.73	(89.88, 104.10)
C_{max} (ng/mL)	6.545	6.539	695.94	691.63	100.62	(93.78, 107.96)

*Geometric means are based on LSM of ln-transformed values.
Source: Table 14.2.1.10

Safety Results: No SAEs were reported over the course of this study. The participation of 2 subjects was discontinued due to AE(s). Subjects 005 and 008 were discontinued due to an AE of vomiting. All subjects who experienced AE(s) during the study recovered completely.

Overall, the most common AEs reported were nausea and dizziness. Nausea was reported on at least one occasion in 6 (6/32) subjects (18.75%) and was considered by the Investigator to be probably related to the treatment. Dizziness was reported on at least one occasion in 5 (5/32) subjects (15.63%) and was geneally considered by the Investigator to be possibly related to the treatment. Palpitations, Vomiting and Hyperhidrosis were reported on at least one occasion in 2 (2/32) subjects (6.25%) and were considered to by the Investigator to be probably related to the treatment.

Conclusions: The results of this study indicate that bioequivalence criteria were met when Apotex Inc.'s Atomoxetine HCl 80 mg Capsules and Strattera 80 mg Capsules were administered under fasted conditions.

Overall, Atomoxetine HCl 80 mg Capsules were well tolerated as a single oral dose of 80 mg (1 × 80 mg capsule.) administered to healthy adult subjects under fasted conditions.

Date of Report (date report issued): 26 March 2012 Final Report Version 1.0