



## **MHRA UK PUBLIC ASSESSMENT REPORT**

### **Atomoxetine: a review of the effects on heart rate and blood pressure**

**May 2012**

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## PLAIN-LANGUAGE SUMMARY

**KEY MESSAGE:** Many patients taking atomoxetine experience increases in heart rate and/or blood pressure. In most patients, these increases are small (<10 beats per minute/<5 mmHg, respectively) and only last a short time. However in approximately 10% of patients, the increases are larger and more prolonged, and may have clinical implications in some patient groups.

Atomoxetine should not be used in patients with pre-existing severe heart or circulation problems (including disorders in the blood circulation system of the brain). Health professionals should monitor blood pressure and heart rate in all patients receiving atomoxetine during the course of their treatment.

It is important to remember that in patients without pre-existing heart or circulation problems, the benefits of atomoxetine outweigh the risks.

### Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency responsible for regulating medicines and medical devices. We continually review the safety of medicines and vaccines in the UK<sup>1</sup>, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses an analysis of the effects of a medicine called atomoxetine on heart rate and blood pressure.

Atomoxetine (brand name Strattera) is a prescription medicine used to treat a condition called attention-deficit and hyperactivity disorder (ADHD)<sup>2</sup> in children aged over 6 years and in adolescents. Some patients may also need to continue atomoxetine treatment into adulthood – this will be advised by their healthcare specialist. Around 32 000 patients in the UK were prescribed atomoxetine between August 2010–July 2011; approximately 46% of these patients were aged 6-12 years, 39% were aged 13-17 years; and 14% were aged 18-55 years<sup>3</sup>.

As with any medicine, the use of atomoxetine may lead to adverse drug reactions (ADRs; side effects) in some individuals. It is already known from clinical study results that many patients taking atomoxetine experience a small increase in heart rate (on average less than 10 beats per minute) and/or a small increase in blood pressure (on average less than 5 mm Hg). For most patients these increases are not clinically important (ie. they are not associated with any clinical adverse event).

However, recent analyses of results from clinical trials along with results from a clinical study suggesting that atomoxetine may cause greater-than-expected increases in blood pressure and/or heart rate in some individuals, led the MHRA and the European [Pharmacovigilance Working Party](#)<sup>4</sup> to conduct a review of all available clinical data to further understand the effects of atomoxetine on blood pressure and heart rate. The results and conclusions from the review are summarised below.

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<sup>1</sup> Suspected side effects to any drug or vaccine can be reported to the MHRA by both healthcare professionals and members of the public via the YellowCard Scheme ([www.yellowcard.mhra.gov.uk](http://www.yellowcard.mhra.gov.uk))

<sup>2</sup> A behavioural disorder characterised by a lack of attention, hyperactivity, and impulsive behaviour

<sup>3</sup> Data obtained from IMS DiseaseAnalyzer-Mediplus

<sup>4</sup> A group which provides recommendations on pharmacovigilance matters to the [Committee for Medicinal Products for Human Use](#) in the [European Medicines Agency](#)

## Results

The review examined information obtained up until 31<sup>st</sup> December 2009 from all clinical trials with atomoxetine. These included results from 8 417 paediatric patients (aged less than 18 years), and 2 170 adult patients (aged 18 years and over).

Analysis of the trial results showed that many patients taking atomoxetine experienced a small increase in heart rate (on average less than 10 beats per minute) and/or a small increase in blood pressure (on average less than 5 mmHg).

However, around 6-12% of atomoxetine patients from controlled and uncontrolled trials experienced clinically important increases in heart rate ( $\geq 20$  beats per minute) or blood pressure ( $\geq 15$ -20 mmHg). Analysis of these clinical trial data showed that approximately 15-32% of patients experiencing clinically relevant changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases.

Although current evidence does not suggest that atomoxetine use is associated with an increased risk of cardiovascular<sup>5</sup> or cerebrovascular<sup>6</sup> adverse effects (eg, heart attack or stroke), the fact that it may cause large sustained increases in heart rate and blood pressure in some individuals has raised concerns. This is because large sustained increases in heart rate or blood pressure may increase the risk of cardiovascular/cerebrovascular clinical conditions occurring in a small proportion of vulnerable or susceptible patients. Such patients include those who have already experienced similar clinical conditions such as a heart attack or stroke.

Therefore, after reviewing all available data on this issue, the MHRA and Pharmacovigilance Working Party recommended the following updates to safety and prescribing information<sup>7</sup> for atomoxetine:

### Key updates:

- Atomoxetine should not be used in patients with pre-existing severe cardiovascular or cerebrovascular disorders, such as: severe hypertension<sup>8</sup>; heart failure; inherited heart conditions or disease; heart attack or stroke<sup>9</sup>; cardiomyopathy<sup>10</sup>; or cerebral aneurysm<sup>11</sup>
- Patients being considered for atomoxetine treatment should be examined by their healthcare provider before starting treatment, to determine whether any cardiac disease is present, and to record their blood pressure and heart rate
- Once treatment with atomoxetine has started, the patient's blood pressure and heart rate should continue to be regularly monitored by their healthcare provider throughout the treatment period

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<sup>5</sup> Related to the heart and blood circulatory system

<sup>6</sup> Blood circulatory system of the brain

<sup>7</sup> Product information for medicines in the UK can be found at [www.emc.co.uk](http://www.emc.co.uk)

<sup>8</sup> High blood pressure

<sup>9</sup> An interruption of blood flow to the brain that results in brain damage, causing symptoms such as weakness on one side of the body, or loss of speech or vision

<sup>10</sup> Deterioration of heart muscle

<sup>11</sup> The rupture or leak of a major blood vessel (artery) in the brain.

- A patient must immediately tell their doctor if they develop any of the following symptoms while taking atomoxetine:
  - Chest pain
  - Shortness of breath
  - Irregular or faster-than-normal heart beat

These symptoms may be signs of a cardiovascular problem.

- Patients who have underlying risk factors for cerebrovascular conditions (eg, a history of cerebrovascular disease or who are using medicines that elevate blood pressure) should have their blood pressure and heart rate checked at every visit by their healthcare provider once atomoxetine treatment has started
- Patients who take atomoxetine for more than a year should have their treatment reviewed at least once a year by a specialist in the treatment of ADHD, who will determine whether continuation of treatment is necessary

The updated information and advice for atomoxetine was communicated in December 2011 in a [letter to appropriate health professionals](#) and an article in [Drug Safety Update](#)<sup>12</sup> (DSU).

Included in both the letter and the DSU article is [a physician's guide for assessing and monitoring cardiovascular risk when prescribing atomoxetine, and a checklist of actions that a health professional should follow before prescribing or administering atomoxetine](#). The use of both the guide and the checklist is strongly recommended for atomoxetine prescribers.

It is important to remember that current evidence does not suggest that atomoxetine use is associated with an increased risk of serious cardiovascular or cerebrovascular outcomes. In patients without pre-existing heart or circulation problems, the benefits of atomoxetine outweigh the risks.

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<sup>12</sup>A monthly MHRA publication for health professionals on the latest safety information for medicines and vaccines

## 1. INTRODUCTION

*(See glossary for an explanation of terms used in this report)*

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. The following report summarises an analysis of the effects of atomoxetine on blood pressure and heart rate.

## 2. BACKGROUND

Atomoxetine (brand name Strattera) is a selective noradrenaline reuptake inhibitor indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years and older, and in adolescents, as part of a comprehensive treatment programme. In addition, for adolescents whose symptoms persist into adulthood who have shown clear benefit from atomoxetine treatment, it may be appropriate to continue treatment into adulthood. However, starting treatment with atomoxetine in adults is not appropriate.

If patients continue treatment with atomoxetine beyond 1 year, re-evaluation of the need for therapy by a specialist in the treatment of ADHD is recommended.

Atomoxetine first became available in the UK in May 2004, and has been prescribed for approximately 191 000 UK patients since this time. 32 000 patients were prescribed atomoxetine in the UK from August 2010–July 2011. Of these, 15 000 were children aged 6-12 years; 12 700 were adolescents aged 13-17 years; and 4 600 were adults aged 19-55 years.<sup>13</sup>

As with any medicine, the use of atomoxetine may cause adverse drug reactions (ADRs) in some individuals. In 2004, results from clinical studies showed that many patients taking atomoxetine experience a modest increase in heart rate (a mean increase of less than 10 beats per minute) and/or blood pressure (a mean increase of less than 5 mmHg). For most patients these changes are not clinically important (ie, they are not associated with an increased risk of clinical problems, such as stroke or myocardial infarction), but patients who already have raised blood pressure or increased heart rate, or a circulatory disease, should take care. The evidence suggested that atomoxetine should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. This information on cardiovascular effects was included in the product information<sup>14</sup> for atomoxetine.

Since 2004, a more recent clinical study ([Beasley and colleagues, 2010](#)) has suggested that atomoxetine may cause greater-than-expected increases in blood pressure and/or heart rate in some individuals. These findings led the MHRA and the European

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<sup>13</sup> Data obtained from IMS Disease Analyzer Mediplus

<sup>14</sup> The Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL) – see <http://www.medicines.org.uk/emc/>

[Pharmacovigilance Working Party](#)<sup>15</sup> to review all available clinical data on the effects of atomoxetine on blood pressure and heart rate. The results and conclusions from the review are summarised in this report.

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<sup>15</sup> A group which provides recommendations on pharmacovigilance matters to the [Committee for Medicinal Products for Human Use](#) in the [European Medicines Agency](#)

### 3. METHODS

An extensive analysis of data from all available clinical studies included in the atomoxetine clinical trial safety database (up to 31<sup>st</sup> December 2009) was performed to determine changes in blood pressure and heart rate in clinical trial patients treated with atomoxetine.

The data was divided into two groups for analysis: group 1 which included patients from placebo- and/or methylphenidate<sup>16</sup>-controlled clinical trials; and group 2 (an 'overall' group) which included all patients who received at least one dose of atomoxetine in any clinical trial, including open-label and non-comparator studies. To investigate any changes in blood pressure and heart rate, categorical and continuous analyses were performed using data from both groups.

#### Categorical analyses

Clinically relevant threshold values for blood pressure and/or heart rate were determined statistically for both absolute changes and for changes from baseline, using data from all placebo-treated trial participants. Using these values, categorical analyses were conducted to determine the proportion of study participants who exceeded these thresholds (eg, a heart rate of >99 beats per minute [beats per minute] that increased by >20 beats per minute from baseline). For the controlled clinical trial database, the proportions of patients exceeding these values were compared between atomoxetine, placebo and an active comparator (methylphenidate).

The categorical analyses of clinically relevant changes provided data on the proportion of patients who:

- had a blood pressure or heart rate measurement that exceeded the calculated absolute value limits (eg, heart rate  $\geq 100$  beats per minute; diastolic blood pressure  $\geq 86$  mmHg in children or  $\geq 95$  mmHg in adults; systolic blood pressure  $\geq 132$  mmHg in children or  $\geq 145$  mmHg in adults)
- had a measurement that exceeded the calculated increase from baseline limit (eg, an heart rate increase of  $\geq 20$  beats per minute; an increase in diastolic blood pressure of  $\geq 17$  mmHg in children or adults; and an increase in systolic blood pressure of  $\geq 20$  mmHg in children or adults)
- simultaneously exceeded both an absolute value limit and a change from baseline value limit (for example, heart rate  $\geq 100$  beats per minute and a heart rate increase of  $\geq 20$  beats per minute).

The categorical analyses included blood pressure and heart rate measurements from all post-baseline visits during study treatment, taking into consideration both the maximum value for each patient during treatment (at 'any visit'), and the final measurement at the endpoint visit to provide an estimation of the degree to which the changes persisted over the period that was assessed.

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<sup>16</sup> Changes in haemodynamic parameters such as heart rate and blood pressure are known outcomes with methylphenidate use

The cases of greatest clinical interest were defined as those where values simultaneously exceeded the statistically determined absolute value limit and change from baseline value limit, especially at endpoint (see table 1)

**Table 1.** Statistically determined limits for blood pressure and heart rate in the paediatric and adult ADHD clinical trial population exposed to placebo.

	<b>Limits</b>	<b>DBP (mmHg)</b>	<b>SBP (mmHg)</b>	<b>HR (beats per minute)</b>
<b>Paediatric (age 6-17 years)</b>	Absolute value limit	<b>86</b>	<b>132</b>	<b>111</b>
	Change from baseline value limit	17.66	19.97	23.07
<b>Adult (age 18-64 years)</b>	Absolute value limit	<b>95</b>	<b>145</b>	<b>99</b>
	Change from baseline value limit (	17.00	21.45	20.56

DBP=diastolic blood pressure; SBP =systolic blood pressure; HR=heart rate; beats per minute=beats per minute;

Over time, the changes in patients who exceeded the clinically relevant thresholds were examined to provide information on persistence of the changes. A sustained or persistent pattern over time was defined as a clear and clinically significant increase from baseline that remained at a sustained or plateaued level close to the maximum effect observed.

### **Risk analysis**

The risk analysis calculated the number of patients treated within the placebo-controlled groups and the 'overall analysis' groups (ie, patients from both 'controlled' and 'uncontrolled' trials) who had heart rate and blood pressure measurements exceeding statistically calculated limits at any timepoint and at study endpoint

Finally, the cumulative risk over time and continuous analyses of heart rate and blood pressure for at least 12 months were also calculated.



## 4 RESULTS

The review examined data obtained up until 31<sup>st</sup> December 2009 from clinical trials with atomoxetine. These included results from 8 417 paediatric patients (aged under 18 years), and 2 170 adult patients (aged 18 years and over).

There was a large amount of variability noted in heart rate and blood pressure measurements collected in all of the studies, both within the patient groups treated with atomoxetine and the patient groups treated with placebo.

### 4.1. Summary of findings:

#### 4.1.1 Patients from controlled studies

*Changes at endpoint (paediatric):* In the studies analysed, a significantly greater percentage of children treated with atomoxetine exceeded both the clinically relevant thresholds for absolute value and change from baseline in diastolic blood pressure (0.74%) and heart rate (2.01%), compared with children who received placebo (0.30% and 0.30%, respectively;  $p < 0.05$ ). Similarly a greater percentage of children treated with atomoxetine exceeded pre-determined thresholds and changes from baseline in systolic blood pressure, compared with children who received placebo (0.39 versus 0.30), although this difference was not significant.

*Changes at endpoint (adult):* There were no significant differences in pre-determined thresholds or pre-determined changes from baseline in diastolic or systolic blood pressure between adults who received either atomoxetine or placebo. However, a significantly greater percentage of adult patients receiving atomoxetine exceeded both the pre-determined threshold and changes from baseline in heart rate (2.58% versus 0.54%,  $p < 0.05$ ).

*Long-term changes (paediatric):* Increases in haemodynamic parameters were also observed over long periods of atomoxetine treatment. Diastolic blood pressure increased from baseline by a mean of 3.66 mmHg after more than 12 months' use. Systolic blood pressure increased from baseline by a mean of 6.48 mmHg after more than 12 months' use. Heart rate increased from baseline by a mean of 7.96 beats per minute after 9 months, then decreased after this time to 3.71 beats per minute above baseline levels.

*Long-term changes (adult):* After more than 12 months' use of atomoxetine, diastolic blood pressure in adult patients increased from baseline by a mean of 2.62 mmHg. Systolic blood pressure increased from baseline by a mean of 3.83 mmHg after more than 12 months' use. Heart rate increased from baseline by a mean of 6.61 beats per minute after 12 months' atomoxetine use.

*Atomoxetine versus methylphenidate (paediatric):* For all three haemodynamic parameters, results for the atomoxetine-treated patients were comparable to those for the methylphenidate patients, with no significant differences (although the proportion of patients exceeding the pre-determined threshold and changes from baseline for heart rate was higher with atomoxetine than with methylphenidate).

#### 4.1.2 Patients from all studies (ie, overall analysis of controlled and uncontrolled data)

*Paediatric:* At the last study visit (or study endpoint), of all children who received at least one dose of atomoxetine in any clinical trial, around 8% experienced an increase in systolic blood pressure of 20 mmHg or more (ie. 8% exceeded the clinically relevant threshold for change from baseline); around 11% experienced an increase in diastolic blood pressure of 15 mmHg or more; and around 12% experienced an increase in heart rate of 20 beats per minute or more.

Of those patients who at any time during the study exceeded both the absolute value and the change from baseline limits, around 26%, 15%, and 22%, had progressive or sustained increases in systolic blood pressure, diastolic blood pressure and heart rate, respectively.

*Adults:* At the last study visit, of all adults who received at least one dose of atomoxetine in any clinical trial, around 6% experienced an increase in systolic blood pressure of 20 mmHg or more; 6.5% experienced an increase in diastolic blood pressure of 15 mmHg or more; and around 10% experienced an increase in heart rate of 20 beats per minute or more.

Of those patients who at any time during the study, exceeded both the absolute and the change from baseline limits, around 27%, 32%, and 27%, had progressive or sustained increases in systolic blood pressure, diastolic blood pressure and heart rate, respectively.

Therefore, the proportion of atomoxetine patients from controlled and uncontrolled trials who, at last study visit, experienced clinically important increases in heart rate or blood pressure ranged from 6-12% of children and adults. Of those patients approximately 15-32% had progressive or sustained increases.

## **4.2 All findings**

Table 2 summarises the proportion of patients from controlled clinical trials who, at the last study visit, exceeded either the absolute value limits (ie, the clinically relevant thresholds), or the change from baseline limit values for diastolic blood pressure, systolic blood pressure, or heart rate, with atomoxetine, methylphenidate or placebo use. Table 3 summarises the mean change (maximum values and endpoint values) for haemodynamic parameters.

**Table 2.** Proportion of patients who, at last study visit (endpoint), exceeded clinically relevant thresholds for haemodynamic parameters in atomoxetine clinical trials

	Paediatric: PBO-controlled		Paediatric MPH controlled		Paediatric: ATX/MPH/PBO			Adult: PBO-controlled		Adult: long-term placebo-controlled	
	ATX	PBO	ATX	MPH	ATX	MPH	PBO	ATX	PBO	ATX	PBO
Number of patients	2287	1334	699	468	351	258	198	737	747	499	383
<b>% of patients exceeding both clinically relevant thresholds for absolute values and changes from baseline value at endpoint</b>											
Diastolic blood pressure	0.74*	0.30	0.29	0.64	0.28	0	0	0.27	0.67	0.40	0
Systolic blood pressure	0.39	0.30	0.72	0	0.57	0	0	0.81	0.54	1.00	0.26
Heart rate	2.01*	0.30	2.72	2.56	2.56*	2.33	0	2.58*	0.54	1.00	0.26

\*=significantly different compared to other treatments in trial group; ATX=atomoxetine; PBO=placebo; MPH=methylphenidate

**Table 3.** Overall summary of mean changes at any time (at maximum value) or at last study visit (endpoint) for diastolic blood pressure, systolic blood pressure and heart rate, after treatment with atomoxetine.

	Paediatric overall	Adult overall
Number of patients	7760	2047
<b>Mean maximum change in haemodynamic parameters</b>		
Diastolic blood pressure (mm Hg)	10.3	7.2
Systolic blood pressure (mm Hg)	10.6	8.8
Heart rate (bpm)	16.3	12.6
<b>Mean change at endpoint in haemodynamic parameters</b>		
Diastolic blood pressure (mm Hg)	2.7	1.9
Systolic blood pressure (mm Hg)	2.3	2.0
Heart rate (bpm)	5.7	5.0

'Overall' columns = all patients (paediatric or adult) who received at least one dose of atomoxetine in a clinical trial (including long-term open label, no comparator trials)

#### **4.2.1 Changes in diastolic blood pressure associated with atomoxetine**

In the paediatric acute placebo-controlled patient group, there was a greater than 2-fold difference between atomoxetine-treated patients and placebo-controlled patients in the proportion who simultaneously exceeded the combined absolute value and change from baseline value limits for diastolic blood pressure at endpoint (table 2). This difference was statistically significant (atomoxetine: 0.74%; placebo: 0.30%;  $p < 0.05$ ).

Although the difference between values for atomoxetine patients and placebo patients was not statistically significant in the Adult Acute Placebo-Controlled ADHD Analysis Group (atomoxetine: 0.27%; placebo: 0.67%) or the Adult Long-Term Placebo-Controlled ADHD Analysis Group (atomoxetine: 0.40%; placebo: 0.00%), this may be because the adult analysis groups were much smaller in size than the paediatric groups.

15.2% of paediatric patients and 31.7% of adult patients, who at any time during the study exceeded both the absolute and the change from baseline limits, demonstrated a temporal pattern of values that could be viewed as progressive or sustained.

In the overall databases (table 3), the mean change to maximum diastolic blood pressure was 10.3 mmHg for paediatric patients and 7.2 mmHg for adult patients with atomoxetine use. The mean change at endpoint was 2.7 mmHg for paediatric patients and 1.9 mmHg for adult patients, respectively.

#### **4.2.2 Changes in systolic blood pressure associated with atomoxetine**

The absolute proportions of all atomoxetine-treated patients who exceeded the combined absolute value limit and change from baseline value limit (the most clinically relevant outcome) for systolic blood pressure at any time, were 5.67% for the paediatric overall group, and 2.95% for the adult overall group.

26.4% of paediatric patients and 26.6% of adult patients, who at any time during the study exceeded both the absolute and the change from baseline limits, demonstrated a temporal pattern of values that could be viewed as progressive or sustained.

In the overall databases (table 3), the mean change to maximum systolic blood pressure was 10.6 mmHg for paediatric patients and 8.8 mmHg for adult patients. At endpoint these values were 2.3 mmHg for paediatric patients and 2.0 mmHg for adult patients.

There were no significant differences between mean changes for atomoxetine-treated patients and placebo-treated patients in either the paediatric or adult placebo-controlled analysis groups.

#### **4.2.3 Changes in heart rate associated with atomoxetine**

12.32% of paediatric atomoxetine-treated patients and 8.39% of adult atomoxetine-treated patients exceeded the combined absolute value limit and change from baseline value limit (the most clinically relevant outcome) of heart rate at endpoint in the analysis of clinical data (table 2).

21.9% of paediatric patients and 26.9% of adult patients, who at any time during the study exceeded both the absolute and the change from baseline limits, demonstrated a temporal pattern of values that could be viewed as progressive or sustained.

In the overall databases (table 3), the mean change to maximum value was an increase of 16.3 beats per minute for paediatric patients and 12.6 beats per minute for adult patients. At endpoint these values were 5.7 beats per minute above baseline values for paediatric patients and 5.0 beats per minute above baseline for adult patients. There were no significant differences between mean changes for atomoxetine-treated patients and placebo-treated patients in either the paediatric or adult placebo-controlled analysis groups.

Table 4 shows the proportions of patients who exceeded approximate limits for haemodynamic changes from baseline that were considered clinically relevant. Approximate limits were added for ease of consideration.

**Table 4.** Proportions of patients in clinical studies with atomoxetine who exceeded close approximate thresholds for clinically relevant changes from baseline for diastolic blood pressure, systolic blood pressure, and heart rate.

Haemodynamic change from baseline (close approximate threshold)	% of paediatric overall database exceeding approximate threshold		% of adult overall database exceeding approximate threshold	
	Maximum (%)	Endpoint (%)	Maximum (%)	Endpoint (%)
Diastolic blood pressure (15 mmHg)	33.14	10.74	15.81	6.50
Systolic blood pressure (20 mmHg)	23.43	7.92	14.24	5.90
Heart rate (20 beats per minutes)	38.80	11.58	25.67	9.77

#### **4.2.4. Mean changes in haemodynamic parameters over time in paediatric patients treated with atomoxetine**

*Diastolic blood pressure:* An initial increase in mean diastolic blood pressure was observed in the first 3 months, then a further small increase after >12 months.

*Systolic blood pressure:* A small but relatively consistent increase in mean systolic blood pressure was observed in the first 12 months

*Heart rate:* An initial and relatively progressive increase in mean heart was observed up to 9 months. After 9 months, mean HR values decreased slightly.

#### **4.2.5 Mean changes in haemodynamic parameters over time in adult patients treated with atomoxetine**

*Diastolic blood pressure:* There was a relatively progressive mean increase in diastolic blood pressure up to 6 months. Diastolic blood pressure values decreased from 6 months to 12 months, then increased slightly again after >12 months.

*Systolic blood pressure:* There was a relatively progressive increase in systolic blood pressure up to 6 months, then a further slight increase after 12 months.

*Heart rate:* Initial increases in mean heart rate were observed in the first 3 months then plateaued up to 12 months. After 12 months, a slight decrease in mean heart rate was observed.

#### **4.2.6 Comparisons of changes associated with atomoxetine and methylphenidate**

There were no significant differences in changes from baseline for diastolic blood pressure, systolic blood pressure or heart rate between paediatric patients treated with atomoxetine, and those treated with methylphenidate. (Haemodynamic values for patients taking either drug were significantly different ( $p < 0.05$ ) compared to those receiving placebo).

#### **4.2.7 Further analyses of data from a study by [Beasley and colleagues, 2010](#).**

Another clinical study with atomoxetine was published more recently ([Beasley and colleagues, 2010](#)). This was a thorough ECG study performed in healthy adult males (ie, who did not have ADHD) who were CYP2D6 poor-metabolisers<sup>17</sup>, and aimed to determine the effects of atomoxetine under conditions where it was likely to be in high concentrations for an extended length of time. Data on blood pressure and heart rate, among other data, was collected from this study, and based on these initial data further analyses from this study were performed to see if there was a dose-response relationship:

*Diastolic blood pressure:* The study examined responses to twice-daily atomoxetine (20 mg or 60 mg) in healthy adult men over the course of 1 day. Increases in diastolic

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<sup>17</sup> Individuals with naturally low levels of the enzyme CYP2D6 in their bodies. As this enzyme breaks down many medicines including atomoxetine, it can be expected that such individuals will have high levels of these medicines circulating in their bodies for a longer length of time than normal.

blood pressure were observed with both low- and high-dose atomoxetine, although the changes were more obvious with the higher dose.

*Systolic blood pressure* : There were smaller increases in systolic blood pressure with atomoxetine than seen for diastolic blood pressure, and the dose response was less obvious; however, there was still a small proportion of subjects who had a sustained increase in systolic blood pressure maintained over the 12 hours of the study day.

*Heart rate*: The change in heart rate was the most pronounced of the changes in haemodynamic parameters measured in this study. Around 90% of study participants had increases greater than 10 beats per minute from baseline, and 50% had increases of 20 beats per minute in both atomoxetine-treatment groups..



## 5. DISCUSSION

There was a large amount of variability in the heart rate and blood pressure measurements collected in the studies, both within the patient groups treated with atomoxetine and the patient groups treated with placebo. However, definite trends emerged upon analysis of all of the data, which are discussed below.

### **Characterisation of mean effects of atomoxetine on blood pressure and heart rate**

When looking at the change from baseline to endpoint for all age groups of ADHD trial patients within atomoxetine treatment groups, the mean change for most of the study participants in both diastolic blood pressure and systolic blood pressure are <5 mmHg, and the mean change in heart rate is <10 beats per minute.

Similarly, for most study participants, the mean changes to maximum values for all age groups in the acute analyses and adults in the long-term analyses group, in terms of differences between atomoxetine-treated patients and placebo-treated patients were also <5 mmHg for both diastolic blood pressure and systolic blood pressure, and <10 beats per minute for heart rate.

These findings are as previously estimated, and reflect information already contained in the Summary of product Characteristics and the Patient Information Leaflet for atomoxetine products, which is as follows: *“Many patients taking atomoxetine experience a modest increase in pulse (mean <10 beats per minute) and/or increases in blood pressure (<5 mmHg).”*

However, approximately 6-12% of children and adults in the trials analysed in this review experienced clinically important changes from baseline in diastolic and systolic blood pressure ( $\geq 15$ -20 mmHg) or heart rate ( $\geq 20$  beats per minute), or both, with atomoxetine treatment. Of those individuals who at any time during the study exceeded both the absolute value and the change from baseline limits, 15-32% showed sustained or progressive increases in blood pressure or heart rate. Therefore, baseline and ongoing monitoring of blood pressure and heart rate in all patients during atomoxetine treatment is of importance.

### **Clinically relevant categorical changes in blood pressure and heart rate**

The categorical analysis showed that the proportion of patients exceeding predetermined limits for clinical significance were greater in atomoxetine analysis groups than in placebo. In addition, atomoxetine and methylphenidate were comparable in terms of the proportion of patients who exceeded thresholds of concern. The range of patients that experienced clinically important changes with atomoxetine is 6-12%.

A small proportion of paediatric and adult patients in all atomoxetine analysis groups showed temporal patterns categorised as progressive or sustained – this was in the range of 15% to 32% of patients who had changes exceeding both absolute value limits and change from baseline limits, and simultaneously had persistent or sustained changes. The absolute numbers of patients in this category is small, but it is these changes that may have clinical implications.

## **Dose-dependency of effects**

There was some evidence from the study by [Beasley and colleagues, 2010](#) to support the conclusion that the effects of atomoxetine in this study population (healthy men who were CYP2D6 poor-metabolisers) on increases in heart rate and diastolic blood pressure may be dose-related. The overall evidence for dose-dependency was less obvious for systolic blood pressure.

## **Consequences of haemodynamic changes with atomoxetine on risk of cardiovascular or cerebrovascular outcomes**

Long-term, persistent or sustained increases in blood pressure or heart rate of a magnitude of  $\geq 15$ -20 mmHg or  $\geq 20$  beats per minute, respectively, as seen in this atomoxetine analysis may be a risk factor for the development of more serious adverse cardiovascular outcomes. However there is no strong evidence from other data sources<sup>18</sup> for an increased risk of adverse clinical cardiovascular or cerebrovascular outcomes with atomoxetine?.

## **Benefits versus risks of atomoxetine**

Atomoxetine is an effective and important treatment for some ADHD patients. The analyses in this review show that the mean effects of atomoxetine on cardiovascular outcomes in the majority of patients remain as already listed in the product information (a mean increase in pulse of <10 beats per minute and in blood pressure of <5 mmHg). This level of increase is not thought to be clinically important, and suggests that the benefit/risk ratio in a large proportion of patients is positive.

However, a proportion (approximately 6-12%) of children and adult patients taking atomoxetine experienced clinically important increases in blood pressure (15-20 mmHg or greater) and heart rate (20 beats per minute or greater). These increases for a proportion of these patients were progressive, sustained or persistent. The consequences of progressive or persistent/sustained changes in blood pressure and heart rate of the clinically relevant magnitudes found in this review could potentially be very serious in a minority of patients – the benefit/risk ratio of atomoxetine for these patients may be negative.

In patients with pre-existing cardiovascular disorders, and in patients with some severe pre-existing cerebrovascular disorders such as cerebral aneurysm or stroke, the risk of experiencing persistent and clinically important changes in heart rate and blood pressure with atomoxetine might outweigh any potential benefit, especially with prolonged treatment. In these patients the use of atomoxetine should be contraindicated.

However, in patients without pre-existing cardiovascular conditions, the benefits of atomoxetine outweigh the risks. There is no data to suggest that with long-term use the observed effects on heart rate and blood pressure cause an increase in cardiovascular or cerebrovascular events.

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<sup>18</sup> Other data sources for this statement are: A multi-phase retrospective US cohort study; a UK Prescription Event Monitoring (PEM) study; and a large cohort study, using multiple healthcare claims data.

## 6. CONCLUSIONS AND RECOMMENDATIONS

Analysis of clinical trial data showed that most patients taking atomoxetine experienced a small increase in heart rate (mean of less than 10 beats per minute) and/or a small increase in blood pressure (mean of less than 5 mmHg). These haemodynamic increases are not clinically important, and the information is already contained in the atomoxetine product information (Summary of Product Characteristics [SPC] and Product Information Leaflet [PIL]).

However, around 6-12% of atomoxetine patients from controlled and uncontrolled trials experienced clinically important increases in heart rate ( $\geq 20$  beats per minute) or blood pressure ( $\geq 15$ -20 mmHg). Analysis of these clinical trial data showed that approximately 15-32% of patients experiencing clinically relevant changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases.

Although current evidence does not suggest that atomoxetine use is associated with an increased risk of clinical cardiovascular or cerebrovascular adverse effects, the fact that it may cause large sustained increases in heart rate and blood pressure in some individuals has raised concerns. It is known that large sustained increases in heart rate or blood pressure may increase the risk of developing serious clinical conditions such as stroke, heart disease, and heart attack in a small proportion of vulnerable or susceptible patients, particularly those who already have underlying disorders of the heart or blood circulatory system, such as hypertension, or pre-existing cerebrovascular disorders such as cerebral aneurysm or stroke.

Therefore, after reviewing all available data on this issue, the MHRA and Pharmacovigilance Working Party recommended the following updates to the safety and prescribing information for atomoxetine:

### Key updates:

- Atomoxetine should not be used in patients with pre-existing severe cardiovascular or cerebrovascular disorders in which clinical deterioration would be expected with clinically important increases in blood pressure ( $\geq 15$ -20 mmHg) or heart rate ( $\geq 20$  beats per minute). Examples of such disorders include: severe hypertension; heart failure; inherited heart conditions or disease; heart attack or stroke; cerebral aneurysm; or cardiomyopathy
- Patients being considered for atomoxetine treatment need a careful history and physical examination to assess any presence of cardiac disease. They should be referred for specialist cardiac evaluation if initial findings suggest such history or presence of cardiac disease.
- Consider the balance of benefits and risks of atomoxetine treatment carefully when treating patients whose underlying medical conditions could be worsened by increased blood pressure or heart rate. These conditions include hypertension or tachycardia
- Before prescribing, the patient's cardiovascular status, including blood pressure and heart rate, should be measured on a centile chart

- Once treatment with atomoxetine has started, the patient's cardiovascular status should continue to be regularly monitored by their healthcare provider throughout the treatment period. Blood pressure and heart rate should be measured and recorded on a centile chart after every dose adjustment, and at least every 6 months
- Patients who develop symptoms that suggest heart disease during atomoxetine treatment should undergo a prompt specialist cardiac evaluation.
- Patients with additional risk factors for cerebrovascular conditions (eg, a history of cardiovascular disease or concomitant use of medicines that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms following treatment initiation with atomoxetine
- Patients who take atomoxetine for extended periods (ie, more than 1 year) should have their treatment reviewed at least once a year by a specialist in the treatment of ADHD to determine whether continuation of treatment is needed.

The updated information and advice for atomoxetine was communicated in December 2011 in a [letter to appropriate health professionals](#) and an article in [Drug Safety Update](#)<sup>19</sup> (DSU).

Included in both the letter and the DSU article is [a physician's guide for assessing and monitoring cardiovascular risk when prescribing atomoxetine, and a checklist of actions that a health professional should follow before prescribing or administering atomoxetine](#). The use of both the guide and the checklist is strongly recommended for atomoxetine prescribers.

It is important to remember that current evidence does not suggest that atomoxetine use is associated with an increased risk of serious cardiovascular or cerebrovascular outcomes, and that in patients without pre-existing cardiovascular conditions the benefits of atomoxetine outweigh the risks.

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<sup>19</sup>A monthly MHRA publication for health professionals on the latest safety information for medicines and vaccines

## 7. GLOSSARY

### **ADHD**

Abbreviation for **Attention-deficit/hyperactivity disorder**, a behavioural disorder characterised by a lack of attention, hyperactivity, and impulsive behaviour

### **Arrhythmia**

An abnormal heartbeat, including where the heart either beats too quickly (**tachycardia**) or too slowly (bradycardia)

### **Arteriosclerosis**

A group of medical conditions characterised by a thickening and hardening of arterial walls, that results in impaired circulation

### **Atomoxetine**

A medicine used to treat attention deficit/hyperactivity disorder (ADHD)

### **Attention-deficit/hyperactivity disorder (ADHD)**

A behavioural disorder characterised by a lack of attention, hyperactivity, and impulsive behaviour

### **Cardiomyopathy**

Deterioration of heart muscle

### **Cardiovascular**

Related to the heart and blood vessels

### **Categorical analyses**

An analysis of data that are separated into distinct categories

### **Centile**

Any point on a scale that divides a set of data into 100 parts

### **Cerebral aneurysm**

The rupture or leak of a major blood vessel (artery) in the brain. A large aneurysm can be serious and potentially cause a **stroke** or death.

### **Cerebrovascular**

Related to the blood vessels of the brain

### **Cerebrovascular accident**

The sudden death of some brain cells due to a lack of oxygen when blood flow to the brain is impaired by a blockage or rupture of an artery (also known as a **stroke**)

### **Concomitant medicines**

Two or more medicines given in the same period

### **Congestive heart failure**

A medical condition where the heart pumps ineffectively, causing fluid to collect in the lungs

### **Coronary**

Related to the arteries of the heart

**CYP2D6**

An enzyme in the body which breaks down many medicines, including atomoxetine

**CYP2D6 poor-metabolisers**

Individuals who naturally have low levels of **CYP2D6** in their bodies. As CYP2D6 breaks many medicines down, these individuals may therefore have high levels of these medicines circulating in the body for longer than normal.

**Diastolic blood pressure**

Blood pressure measured during diastole (ie, when the lower chambers of the heart are relaxed and filling with blood)

**Haemodynamic parameters**

Forces that affect the flow of blood around the body; eg, heart rate and blood pressure.

**Heart rate**

Number of heart beats per minute

**Hypertension**

High blood pressure

**Hypertensive crisis**

A severe increase in blood pressure that can lead to a stroke

**Median**

A statistical average: the middle value in a range of values in a sample

**Methylphenidate**

A stimulant drug used to treat **ADHD**

**Mortality**

The incidence of death (or death rate) in a group or population over a given period

**Myocardial infarction**

Death of a segment of heart muscle after its blood supply is interrupted due to a blood clot in an artery (also known as a heart attack)

**Placebo**

Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

**Prescription Event Monitoring study**

A study that monitors the safety of newly licensed medicines using questionnaires completed by general practitioners

**Renal**

Related to the kidney

**Retrospective cohort study**

A study in which the history of a group of individuals with a particular disease or condition is examined for a particular outcome, usually using their medical records for information

**Risk analysis**

An analysis of data to discover a substance or activity that increases the likelihood of an individual developing a particular illness or medical condition

**Selective noradrenaline reuptake inhibitor**

A class of drugs used to treat depression and other conditions, including **ADHD**

**Stroke**

An interruption of blood flow to the brain that results in brain damage, causing symptoms such as weakness on one side of the body, or loss of speech or vision

**Systolic blood pressure**

Blood pressure measured during systole (ie. when the heart contracts and forces blood out)

**Tachycardia**

An abnormal increase in heart rate

**Temporal**

Related to time (eg, the timing of when a drug is taken)

**Transient ischaemic attack**

A temporary interruption of blood flow to the brain which causes symptoms similar to a **stroke** (although the symptoms don't last as long)

**Ventricular arrhythmia**

An abnormal heart rate caused by a disturbance in the lower chambers of the heart

**Ventricular hypertrophy**

An enlargement of the lower chambers in the heart