

# Effects of Strattera (atomoxetine) on blood pressure and heart rate from review of MAH clinical trial database.

Final SmPC and PL wording agreed by PhVWP November 2011

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## SUMMARY OF PRODUCT CHARACTERISTICS

### *Posology and method of administration*

(.....)

#### Pre-treatment screening:

Prior to prescribing it is necessary to take an appropriate medical history and conduct a baseline evaluation of a patients cardiovascular status, including blood pressure and heart rate (see Sections 4.3 and 4.4).

#### Ongoing monitoring:

Cardiovascular status should be regularly monitored with blood pressure and pulse recorded on a centile chart after each adjustment of dose and then at least every 6 months (see Section 4.4).

### *4.3 Contraindications*

(.....)

Atomoxetine should not be used in patients with severe cardiovascular disorders or cerebrovascular whose condition would be expected to deteriorate if they experienced increases in blood pressure or heart rate that could be clinically important (for example, 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate) [See 4.4 Special Warnings and Special Precautions for Use – Cardiovascular Effects]. Severe cardiovascular disorders may include severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels). Severe cerebrovascular disorders may include cerebral aneurysm or stroke.

- (.....)

### *4.4 Special warnings and precautions for use*

.....

#### Cardiovascular effects

Atomoxetine can ~~effect~~-affect heart rate and blood pressure.

~~Many~~-Most patients taking atomoxetine experience a modest increase in ~~pulse~~-heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) that may not be clinically important (see section 4.8). ~~For most patients, these changes are not clinically important.~~

However, data from ADHD clinical trials show that some patients (approximately 6-12% of children and adults) experience clinically relevant changes in heart rate (20 beats per minute or greater) and blood pressure (15-20 mmHg or greater). Analysis of these clinical trial data showed that approximately 12-32% of patients experiencing clinically relevant changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases.

As a result of these findings, patients who are being considered for treatment with atomoxetine should have a careful history and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease.

It is recommended that heart rate and blood pressure be measured and recorded on a centile chart before treatment is started and, during treatment, after each adjustment of dose and then at least every 6 months to detect possible clinically important increases.

Atomoxetine should not be used in patients with severe cardiovascular or cerebrovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or heart rate that could be clinically important (See section 4.3 Contraindications – Severe Cardiovascular And Cerebrovascular Disorders).~~Pulse and blood pressure should be measured periodically while on therapy.~~ Atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure and heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.

Patients who develop symptoms suggestive of cardiac disease during atomoxetine treatment should undergo a prompt specialist cardiac evaluation.

~~Atomoxetine~~ In addition, atomoxetine should be used with caution in patients with congenital or acquired long QT or a family history of QT prolongation (see sections 4.5 Interactions and 4.8 Undesirable Effects).

~~Orthostatic~~ As orthostatic hypotension has also been reported,~~Use,~~ atomoxetine should be used with caution in any condition that may predispose patients to hypotension or conditions associated with abrupt heart rate or blood pressure changes.

### Cerebrovascular effects

Patients with additional risk factors for cerebrovascular conditions (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with atomoxetine.

(.....)

### **4.5 Interaction with other medicinal products and other forms of interaction**

(.....)

### Anti-hypertensive drugs

Atomoxetine should be used cautiously with antihypertensive drugs. Because of a possible increase in blood pressure, atomoxetine may decrease the effectiveness of antihypertensive drugs / drugs used to treat hypertension. Attention should be paid to monitoring of blood pressure and

review of treatment of atomoxetine or antihypertensive drugs may be justified in the case of significant changes of blood pressure.

**Pressor agents or drugs that increase blood pressure**

Because of possible increase in effects on blood pressure, atomoxetine should be used cautiously with pressor agents or medications that may increase blood pressure (such as salbutamol). Attention should be paid to monitoring of blood pressure, and review of treatment for either atomoxetine or pressor agents may be justified in the case of significant change in blood pressure.

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(.....)

**4.8 Undesirable effects**

Children and adolescents:

(.....)

In both paediatric and adult placebo-controlled trials, patients taking atomoxetine experienced increases in heart rate, of about 6 beats/minute and mean increases in systolic and diastolic blood pressure of about 2 mm Hg compared with placebo. ~~In adult placebo-controlled trials, patients taking atomoxetine experienced a mean increase in heart rate of 5 beats/minute and mean increases in systolic (about 2 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo.~~ (see section 4.4 – Special Warnings and Precautions).

Table: Adverse reactions

Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), data from spontaneous reports (frequency not known – cannot be estimated from the available data).

System Class	Organ	Very common	Common	Uncommon	Post marketing experience Spontaneous reports. *
Investigations		<u>Blood pressure increased<sup>4</sup>, Heart rate increased<sup>4</sup></u>	Weight decreased, <del>blood pressure increased.</del>		

<sup>4</sup> Heart rate and blood pressure findings are based on measured vital signs.

Adults:

Table: Adverse reactions

Frequency estimate: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), data from spontaneous reports (frequency not known – cannot be estimated from the available data).

System Class	Organ	Very common	Common	Uncommon	Post-marketing experience Spontaneous reports. *
Investigations		Blood pressure increased <sup>3</sup> , Heart rate increased <sup>3</sup>	Weight decreased	Blood pressure increased	

<sup>3</sup> Heart rate and blood pressure findings are based on measured vital signs.

### 5.1 Pharmacodynamic properties

.....)

A thorough QT/QTc study, conducted in healthy adult CYP2D6 poor metabolizer (PM) subjects dosed up to 60mg of atomoxetine BID, demonstrated that at maximum expected concentrations the effect of atomoxetine on QTc interval was not significantly different from placebo. There was a slight increase in QTc interval with increased atomoxetine concentration.

## **FINAL AGREED CHANGES TO PACKAGE LEAFLET WORDING (RELEVANT SECTIONS ONLY)**

### **2. BEFORE YOU TAKE STRATTERA**

#### **Do not take Strattera**

- if you have serious problems with your heart which may be affected by an increase in heart rate and/or blood pressure, as this may be an effect of Strattera.
- you have serious problems with the blood vessels in your brain - such as a stroke, swelling and weakening of part of a blood vessel (aneurysm) or narrow or blocked blood vessels

**Strattera should not be used in children under six years of age.**

#### **Take special care with Strattera**

Your doctor should measure your blood pressure and your heart rate (pulse) before and during the time you take Strattera.

Talk to your doctor before taking Strattera.

- if you have or had liver problems. You may need a lower dose.
- if you have high blood pressure. Strattera can increase blood pressure.
- if you have problems with your heart (including heart defects) or an increased heartbeat. Strattera can increase your heart rate (pulse). Sudden death has been reported in patients with heart defects.
- if you have low blood pressure. Strattera can cause dizziness or fainting in people with low blood pressure.
- if you have problems with sudden changes in your blood pressure or your heart rate
- if you have a cardiovascular disease or past medical history of stroke.
- if you have a history of epilepsy or have had seizures for any other reason. Strattera might lead to an increase in seizure frequency.

There is a possibility of rare, serious psychiatric adverse effects including psychotic reactions (such as believing things that are not true or being suspicious), hallucinations (such as hearing voices or seeing things which are not there), mania (feeling elated or over-excited, which causes unusual behaviour) and agitation.

#### **Taking other medicines**

(.....)

If you take Strattera at the same time as some other medicines (see examples below), the treatment with these medicines or Strattera may be affected and so caution is needed.

- medicines that increase blood pressure or used to control blood pressure . Strattera can alter blood pressure.

(.....)

### **4. POSSIBLE SIDE EFFECTS**

Like all medicines, Strattera can cause side effects, although not everybody gets them.

(.....)

**Side effects reported in clinical trials of Strattera in teenagers and children over six years old**

Very common side effects (affects more than 1 user in 10) are:

- increased heart rate (pulse)
- increased blood pressure

Other common side effects (affects 1 to 10 users in 100) may be:

~~—increased blood pressure~~

**Side effects reported in clinical trials of Strattera in adults**

- increased blood pressure
- increased heart rate (pulse)

Side effects which have been seen, but are uncommon (affects 1 to 10 users in 1,000), are:

~~—increased blood pressure~~