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**IMPORTANT SAFETY INFORMATION ON STRATTERA (ATOMOXETINE) AND RISKS OF
INCREASED BLOOD PRESSURE AND HEART RATE**

Dear Healthcare Professional,

In agreement with the Irish Medicines Board, Eli Lilly and Company would like to inform you of new clinically important information about the known risks of increased blood pressure and increased heart rate with the use of STRATTERA (atomoxetine) for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

Summary

STRATTERA can affect heart rate and blood pressure. Please be aware of the following new strengthened recommendations:

- STRATTERA 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 in 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 below for further information.
- STRATTERA should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.
- It is recommended that patients who are being considered for treatment with STRATTERA should have a careful history and physical examination to assess for the presence of cardiac disease. Patients should be referred for specialist cardiac evaluation if initial findings suggest such history or presence of cardiac disease.
- Heart rate and blood pressure be measured and recorded (e.g. on a centile chart) in all patients before treatment with STRATTERA is started as well as after each adjustment of dose and then at least every 6 months during treatment to detect possible clinically important increases. If patients develop symptoms suggestive of cardiac disease during treatment they should be referred for prompt specialist cardiac evaluation.

Answers That Matter.

Further information on the safety concern

A recent analysis of combined data from controlled and uncontrolled Lilly sponsored STRATTERA clinical trials has indicated that a proportion of patients (approximately 6 to 12% of children and adults) experience clinically important changes in heart rate (20 beats per minute or greater) or blood pressure (15 to 20 mm Hg or greater). Analysis of these clinical trial data also showed that approximately 15 to 32% of patients experiencing clinically relevant changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases.

The same analysis showed that the hemodynamic changes observed during atomoxetine treatment were similar to those observed during methylphenidate treatment.

The magnitude of the increase in blood pressure and heart rate could be a potential risk in patients with severe cardiovascular or cerebrovascular disorders. Some examples of patients who would be expected to experience critical deterioration in their preexisting condition would include those with the following conditions: severe hypertension, advanced heart failure or arterial occlusive disease, progressive unstable angina, haemodynamically significant congenital heart disease or cardiomyopathies, recent or repeated myocardial infarction, and potentially life-threatening arrhythmias, channelopathies (disorders caused by the dysfunction of ion channels), cerebral aneurysm and stroke.

Hence, Eli Lilly and Company has decided to recommend changes to the prescribing information as highlighted above. The relevant sections of the Summary of Product Characteristics reflecting these changes are provided in Annex 1 (the full SPC is available from:

<http://www.medicines.ie/medicine/11666/SPC/Strattera/> or Lilly Ireland via 01 6614377.

A Physician's Guide to Prescribing and additional tools that should be used for cardiovascular screening and monitoring of patients, are provided in Annex 2. In addition these materials may be requested from Lilly Ireland via 01 6614377.

For further information on managing adverse effects of medication for ADHD, please follow the *European Guidelines* which can be downloaded from:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012210/>

Call for reporting of suspected adverse reactions

Healthcare professionals are reminded of the need to report any adverse events suspected to be associated with the use of STRATTERA to Irish Medicines Board,

Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2,
Ireland.
Tel: 01-676 4971/76
Fax: 01-676 7836
Email: imb@imb.ie

or by using the on-line adverse reaction form on the IMB website at www.imb.ie

Adverse events can also be reported to the Lilly Global Patient Safety department by phoning 01-664-0446.

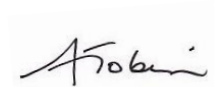
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Communication information

Please contact the Lilly Medical Information Department by phoning 01- 664 -0446 or myself in the Lilly Medical Department, Lilly Ireland, Hyde House, 65 Adelaide Road, Dublin 2, Telephone 01 6614377 if you have questions or if you wish to receive further information.

Yours Faithfully,



Dr. Anne Tobin
Medical Manager
Lilly Ireland

Annexes:

1. Updated sections of SPC
2. Physician's Guide to Prescribing and additional tools that should be used for cardiovascular screening and monitoring of patients

New Text in Strattera (Atomoxetine) SPC in relation to Cardiovascular Disease

New text in underline

Description: *Two Paragraphs added to section 4.2 to advise on pre-treatment screening and ongoing monitoring.*

4.2 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).

Description: *Contraindication added to section 4.3*

4.3 Contraindications

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 (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.

Description: *New information about clinically relevant changes in blood pressure and heart rate and new warnings and precautions related to this data.*

4.4 Special warnings and precautions for use

Cardiovascular effects

Atomoxetine can affect heart rate and blood pressure.

Most patients taking atomoxetine experience a modest increase 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).

However, combined data from controlled and uncontrolled 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 15-32% 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). 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.

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).

As orthostatic hypotension has also been reported, 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.

Description: *New paragraphs to describe possible interaction of atomoxetine with anti-hypertensive drugs*

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.

Description: *New sentence to describe clinical data on heart rate and blood pressure.*

4.8 Undesirable effects

In both paediatric and adult placebo-controlled trials, patients taking atomoxetine experienced increases in heart rate, systolic and diastolic blood pressure (see section 4.4 – Special Warnings and Precautions).

Description: *New paragraph introduced to describe results of clinical QTc study*

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.

Physician's guide for assessing and monitoring cardiovascular risk when prescribing Strattera

Strattera is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older and in adolescents as part of a comprehensive treatment programme.

Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 (<http://www.who.int/classifications/icd/en/bluebook.pdf>)

Treatment must be initiated by a specialist in the treatment of ADHD.

A comprehensive treatment programme typically includes psychological, educational and social measures and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractability, 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 children with this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity of the child's symptoms in relation to the child's age and the persistence of symptoms.

Full information on the safety and efficacy of Strattera is provided in the Summary of Product Characteristics (See www.medicines.org.uk/emc).

This guide provides specific information for prescribing physicians in regard to prescreening and ongoing monitoring of cardiovascular safety.

Physicians should be aware that Strattera can affect heart rate and blood pressure. Patients who are being considered for treatment with Strattera should have a careful history (including assessment of concomitant medications, past and present co-morbid medical disorders or symptoms as well as any family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical exam to assess for the presence of cardiac disease. Patients should be referred for further specialist cardiac evaluation if initial findings suggest such history or disease.

It is further 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 be used cautiously with antihypertensive drugs and with pressor agents or medications that may increase blood pressure (such as salbutamol).

The tools provided in this guide should help appropriate screening and monitoring of patients.

Strattera should be used in accordance with national clinical guidance on treatment of ADHD where available. Where patients are continuing treatment with atomoxetine beyond 1 year, re-evaluation of the need for therapy by a specialist in the treatment of ADHD is recommended.

Checklist for actions to take before prescribing / dispensing or administering Strattera

Patient's ID _____ Date _____

A specialist in the treatment of ADHD has made the initial diagnosis for your patient according to DSM criteria or guidelines in ICD.

A comprehensive medical history has been performed, including:

– Concomitant medications: _____

Note that atomoxetine should be used cautiously with antihypertensive drugs and with pressor agents or medications that may increase blood pressure, such as salbutamol

– Family history: _____

Note that a family history of sudden cardiac/unexplained death or malignant arrhythmia is a risk factor for cardiovascular outcomes

– Past and present co-morbid medical disorders or symptoms: _____

Physical examination has been performed

Notes: _____

A baseline evaluation of the patient's cardiovascular status has been made, including measurement of blood pressure and heart rate

(For children, it is recommended that these measurements are recorded on a centile chart, if a centile chart is not available, recordings may be made in the attached chart.)

Evaluation shows an absence of severe cardiovascular or cerebrovascular disorder which would be expected to deteriorate if the patient experiences clinically important increases in blood pressure or in heart rate (for example, 15 to 20 mm Hg increase in blood pressure or 20 beats per minute increase in heart rate).

– *Some examples of patients who would be expected to experience critical deterioration in their preexisting condition would include those with the following conditions: Severe cardiovascular diseases include severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias, channelopathies (disorders caused by the dysfunction of ion channels), cerebral aneurysm and stroke.*

Initial findings from the patient's history and physical examination do not suggest any cardiovascular or cerebrovascular disease

check one

OR

Initial findings from the patient's history and physical examination suggest a cardiovascular or cerebrovascular disease and a cardiac specialist has advised that treatment with Strattera may be initiated under careful monitoring.

All boxes should be checked before you proceed further to start treatment in your patient

Checklist for monitoring to manage cardiovascular risks with Strattera treatment

Patient's ID _____ Date _____

If it has been 6 months since your patient's last assessment or if you have adjusted their dose, blood pressure and heart rate have been measured and recorded
(For children, it is recommended that these measurements are recorded on a centile chart, if a centile chart is not available, recordings may be made in the attached chart.)

Notes: _____

Your patient has NOT developed signs/symptoms of new cardiovascular disorder or worsening of a pre-existing cardiovascular disorder *check one*

OR

Your patient has developed signs/symptoms of new cardiovascular disorder or worsening of a pre-existing cardiovascular disorder and after further investigation a cardiac specialist has advised that treatment with Strattera may be continued

Notes _____

Your patient has NOT developed new neurologic signs/symptoms *check one*

OR

Your patient has developed new neurologic signs/symptoms and specialist has advised that treatment with Strattera may be continued

Notes _____

Your patient has been on treatment with atomoxetine for less than 1 year *check one*

OR

Your patient has been on treatment with atomoxetine for more than 1 year, and a re-evaluation of the need for therapy by a specialist in the treatment of ADHD has been conducted

Note _____

A check should be made in each box at every visit during treatment

