

The following table contains language from ADHD labeling regarding cardiovascular events in the following sections of labeling: **Black Box, Contraindications, Warnings, and Precautions.** (search terms: cardiovascular, heart, heart rate, sudden death, blood pressure) Adverse events not listed per meeting.

| Drug/NDA#  | Black Box | Contraindications | Warnings   | Precautions   |
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| Concerta (methylphenidate HCL) Extended-Release Tablets; NDA 21-121    | N/A       | N/A               | <p><b>Hypertension and other Cardiovascular Conditions</b><br/>           Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, eg, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking CONCERTA®, especially patients with hypertension.</p> <p>In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo.</p> <p>In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.</p> | <p><b>Precautions/Drug Interactions</b><br/>           Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents.</p>  |
| Ritalin LA (methylphenidate HCL) Extended-Release Capsules; NDA 21-284 | N/A       | N/A               | <p><b>Hypertension and other Cardiovascular Conditions</b><br/>           Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking Ritalin LA, especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure</p>  | <p><b>Precautions/Drug Interactions</b><br/>           Methylphenidate may decrease the hypotensive effect of guanethidine. Because of possible effects on blood pressure, methylphenidate should be used cautiously with pressor agents.</p> |

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|  |     |  | or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, cardiac arrhythmia, or hyperthyroidism.  |   |
| Ritalin and Ritalin SR (combined label) (methylphenidate HCL) Tablets and Sustained-Release Tablets; NDA 10-187 and NDA 18-029 respectively. | N/A | N/A  | Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking Ritalin especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, cardiac arrhythmia, or hyperthyroidism.  |   |
| Metadate CD (methylphenidate HCL) Extended-Release Capsules; NDA 21-259  | N/A | <b>Hypertension and Other Cardiovascular Conditions:</b> METADATE CD is contraindicated in patients with severe hypertension, angina pectoris, cardiac arrhythmias, heart failure, recent myocardial infarction, hyperthyroidism or thyrotoxicosis (see WARNINGS). | <b>Hypertension and other Cardiovascular Conditions:</b> Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking METADATE CD, especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension (see CONTRAINDICATIONS).   | <b>Drug Interactions:</b> Because of possible effects on blood pressure, METADATE CD should be used cautiously with pressor agents.   |
| Focalin (dexmethylphenidate HCL) Tablets; NDA 21-278   | N/A | N/A  | <b>Hypertension and Other Cardiovascular Conditions</b><br>Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Focalin, especially those with hypertension. In the placebo controlled studies, the mean pulse increase was 2-5 bpm for both Focalin and racemic methylphenidate compared to placebo, with mean increases of systolic and diastolic blood pressure of 2-3 mmHg, compared to placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent | <b>Precautions/Drug Interactions</b><br>Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. Because of possible effects on blood pressure, Focalin should be used cautiously with pressor agents. |

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|  |   |  | myocardial infarction, cardiac arrhythmia, or hyperthyroidism.  |  |
| Focalin XR<br>(dexamethylphenidate HCL)<br>Extended-Release Capsules;<br>NDA 21-802                    | N/A   | N/A  | <b>Hypertension and Other Cardiovascular Conditions</b><br>Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with preexisting hypertension, heart failure, recent myocardial infarction, cardiac arrhythmia or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking Focalin XR, especially patients with hypertension. Studies of Focalin XR and methylphenidate have shown small, mean, dose-related, increases of resting pulse and blood pressure in both pediatric patients and adults. | <b>Precautions/Drug Interactions</b><br>Because of possible effects on blood pressure, Focalin XR should be used cautiously with pressor agents. Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.   |
| Adderall (mixed salts of a single entity amphetamine product) Tablets; NDA 11-522                      | MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS. | Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.<br>Agitated states. | <b>Sudden Death and Pre-existing Structural Cardiac Abnormalities:</b> Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall generally should not be used in children or adults with structural cardiac abnormalities.  | Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Blood pressure and pulse should be monitored at appropriate intervals in patients taking Adderall, especially patients with hypertension.<br><br>ADVERSE REACTIONS:<br>Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use                    |
| Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules; NDA 21-303 | MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS. | Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.                     | <b>Sudden Death and Pre-existing Structural Cardiac Abnormalities:</b> Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR® generally should not be used in children, adolescents, or adults with structural cardiac abnormalities.  | Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR®, especially patients with hypertension.<br><br>Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication.<br><br>In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood |

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|  |     |     |     | <p>pressure elevations <math>\geq 15</math> mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving ADDERALL XR® 10 or 20 mg. Isolated elevations in diastolic blood pressure <math>\geq 8</math> mmHg were observed in 16/64 (25%) placebo-treated patients and 22/100 (22%) ADDERALL XR®-treated patients. Similar results were observed at higher doses.</p> <p>In a single-dose pharmacokinetic study in 23 adolescents, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg ADDERALL XR®, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours post dose and not associated with symptoms.</p> |
| Strattera (atomoxetine HCL) Capsules; NDA 21-411 | N/A | N/A | N/A | <p>General<br/>Effects on blood pressure and heart rate — STRATTERA should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because it can increase blood pressure and heart rate. Pulse and blood pressure should be measured at baseline, following STRATTERA dose increases, and periodically while on therapy.</p> <p>In pediatric placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of about 6 beats/minute compared with placebo subjects. At the final study visit before drug discontinuation, 3.6% (12/335) of STRATTERA-treated subjects had heart rate increases of at least 25 beats/minute and a heart rate of at least 110 beats/minute, compared with 0.5% (1/204) of placebo</p>  |

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|  |  |  |  | <p>subjects. No pediatric subject had a heart rate increase of at least 25 beats/minute and a heart rate of at least 110 beats/minute on more than one occasion.</p> <p>Tachycardia was identified as an adverse event for 1.5% (5/340) of these pediatric subjects compared with 0.5% (1/207) of placebo subjects. The mean heart rate increase in extensive metabolizer (EM) patients was 6.7 beats/minute, and in poor metabolizer (PM) patients 10.4 beats/minute.</p> <p>STRATTERA-treated pediatric subjects experienced mean increases of about 1.5 mm Hg in systolic and diastolic blood pressures compared with placebo. At the final study visit before drug discontinuation, 6.8% (22/324) of STRATTERA-treated pediatric subjects had high systolic blood pressure measurements compared with 3.0% (6/197) of placebo subjects. High systolic blood pressures were measured on 2 or more occasions in 8.6% (28/324) of STRATTERA-treated subjects and 3.6% (7/197) of placebo subjects. At the final study visit before drug discontinuation, 2.8% (9/326) of STRATTERA-treated pediatric subjects had high diastolic blood pressure measurements compared with 0.5% (1/200) of placebo subjects. High diastolic blood pressures were measured on 2 or more occasions in 5.2% (17/326) of STRATTERA-treated subjects and 1.5% (3/200) of placebo subjects. (High systolic and diastolic blood pressure measurements were defined as those exceeding the 95th percentile, stratified by age, gender, and height percentile - National High Blood Pressure Education Working Group on Hypertension Control in Children and Adolescents.)</p> <p>In adult placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of 5 beats/minute compared with placebo subjects.</p> |
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|   |     |     |   | <p>Tachycardia was identified as an adverse event for 3% (8/269) of these adult atomoxetine subjects compared with 0.8% (2/263) of placebo subjects.</p> <p>STRATTERA-treated adult subjects experienced mean increases in systolic (about 3 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo. At the final study visit before drug discontinuation, 1.9% (5/258) of STRATTERA-treated adult subjects had systolic blood pressure measurements <math>\geq</math>150 mm Hg compared with 1.2% (3/256) of placebo subjects. At the final study visit before drug discontinuation, 0.8% (2/257) of STRATTERA-treated adult subjects had diastolic blood pressure measurements <math>\geq</math>100 mm Hg compared with 0.4% (1/257) of placebo subjects. No adult subject had a high systolic or diastolic blood pressure detected on more than one occasion.</p> <p>Orthostatic hypotension has been reported in subjects taking STRATTERA. In short-term, child- and adolescent-controlled trials, 1.8% (6/340) of STRATTERA-treated subjects experienced symptoms of postural hypotension compared with 0.5% (1/207) of placebo-treated subjects. STRATTERA should be used with caution in any condition that may predispose patients to hypotension.</p> |
| Methylin (methylphenidate HCL) Chewable Tablets; NDA 21-475 | N/A | N/A | Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Methylin®, especially those with hypertension. | N/A   |
| Methylin (methylphenidate HCL) Oral Solution; NDA           | N/A | N/A | Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking  | N/A   |

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| 21-419   |  |   | Methylin®, especially those with hypertension. |   |
| Dexedrine<br>(dextroamphetamine sulfate)<br>Spansule Capsules; NDA<br>17-078 |  | Advanced arteriosclerosis,<br>symptomatic cardiovascular<br>disease, moderate to severe<br>hypertension, hyperthyroidism,<br>known hypersensitivity or<br>idiosyncrasy to the<br>sympathomimetic amines,<br>glaucoma. |  | <b>Adverse Reactions/Cardiovascular:</b> Palpitations,<br>tachycardia, elevation of blood pressure. There have<br>been isolated reports of cardiomyopathy associated<br>with chronic amphetamine use. |