

STRATTERA[®]

(atomoxetine HCl)

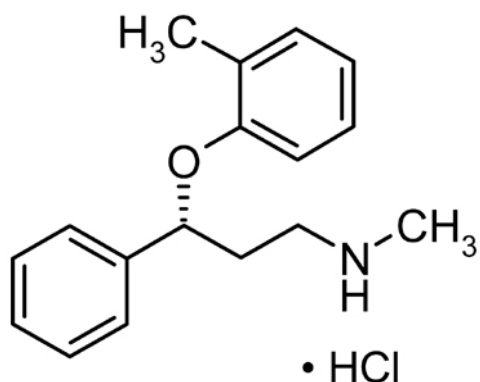
WARNING

Suicidal Ideation in Children and Adolescents — STRATTERA (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of STRATTERA in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. STRATTERA is approved for ADHD in pediatric and adult patients. STRATTERA is not approved for major depressive disorder.

Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of STRATTERA in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA compared to placebo. The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials. (See WARNINGS and PRECAUTIONS, Pediatric Use).

DESCRIPTION

STRATTERA[®] (atomoxetine HCl) is a selective norepinephrine reuptake inhibitor. Atomoxetine HCl is the *R*(-) isomer as determined by x-ray diffraction. The chemical designation is (-)-*N*-Methyl-3-phenyl-3-(*o*-tolylloxy)-propylamine hydrochloride. The molecular formula is C₁₇H₂₁NO•HCl, which corresponds to a molecular weight of 291.82. The chemical structure is:



Atomoxetine HCl is a white to practically white solid, which has a solubility of 27.8 mg/mL in water.

STRATTERA capsules are intended for oral administration only.

Each capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, 60, 80, or 100 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain one or more of the following: FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide, red iron oxide. The capsules are imprinted with edible black ink.

CLINICAL PHARMACOLOGY

36

37 **Pharmacodynamics and Mechanism of Action**

38 The precise mechanism by which atomoxetine produces its therapeutic effects in Attention-
39 Deficit/Hyperactivity Disorder (ADHD) is unknown, but is thought to be related to selective
40 inhibition of the pre-synaptic norepinephrine transporter, as determined in ex vivo uptake and
41 neurotransmitter depletion studies.

42 **Human Pharmacokinetics**

43 Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is
44 eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6)
45 enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about
46 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are
47 poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity
48 in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and
49 slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people
50 with normal activity [extensive metabolizers (EMs)]. Drugs that inhibit CYP2D6, such as
51 fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.

52 The pharmacokinetics of atomoxetine have been evaluated in more than 400 children and
53 adolescents in selected clinical trials, primarily using population pharmacokinetic studies.
54 Single-dose and steady-state individual pharmacokinetic data were also obtained in children,
55 adolescents, and adults. When doses were normalized to a mg/kg basis, similar half-life, C_{max} ,
56 and AUC values were observed in children, adolescents, and adults. Clearance and volume of
57 distribution after adjustment for body weight were also similar.

58 Absorption and distribution — Atomoxetine is rapidly absorbed after oral administration, with
59 absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations
60 (C_{max}) are reached approximately 1 to 2 hours after dosing.

61 STRATTERA can be administered with or without food. Administration of STRATTERA with
62 a standard high-fat meal in adults did not affect the extent of oral absorption of atomoxetine
63 (AUC), but did decrease the rate of absorption, resulting in a 37% lower C_{max} , and delayed T_{max}
64 by 3 hours. In clinical trials with children and adolescents, administration of STRATTERA with
65 food resulted in a 9% lower C_{max} .

66 The steady-state volume of distribution after intravenous administration is 0.85 L/kg indicating
67 that atomoxetine distributes primarily into total body water. Volume of distribution is similar
68 across the patient weight range after normalizing for body weight.

69 At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily
70 albumin.

71 Metabolism and elimination — Atomoxetine is metabolized primarily through the CYP2D6
72 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma
73 concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC
74 of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. Laboratory
75 tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent
76 inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial
77 increase in atomoxetine plasma exposure, and dosing adjustment may be necessary (*see*
78 Drug-Drug Interactions). Atomoxetine did not inhibit or induce the CYP2D6 pathway.

79 The major oxidative metabolite formed, regardless of CYP2D6 status, is
80 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to
81 atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much

82 lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine
83 concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs,
84 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes.
85 N-Desmethyatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has
86 substantially less pharmacological activity compared with atomoxetine and circulates in plasma
87 at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine
88 concentration in PMs).

89 Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is
90 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to
91 PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs,
92 AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. The
93 elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethyatomoxetine (6 to
94 8 hours) in EM subjects, while the half-life of N-desmethyatomoxetine is much longer in PM
95 subjects (34 to 40 hours).

96 Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-*O*-glucuronide, mainly in the
97 urine (greater than 80% of the dose) and to a lesser extent in the feces (less than 17% of the
98 dose). Only a small fraction of the STRATTERA dose is excreted as unchanged atomoxetine
99 (less than 3% of the dose), indicating extensive biotransformation.

100 **Special Populations**

101 Hepatic insufficiency — Atomoxetine exposure (AUC) is increased, compared with normal
102 subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe
103 (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is
104 recommended for patients with moderate or severe hepatic insufficiency (*see* DOSAGE AND
105 ADMINISTRATION).

106 Renal insufficiency — EM subjects with end stage renal disease had higher systemic exposure
107 to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when
108 exposure was corrected for mg/kg dose. STRATTERA can therefore be administered to ADHD
109 patients with end stage renal disease or lesser degrees of renal insufficiency using the normal
110 dosing regimen.

111 Geriatric — The pharmacokinetics of atomoxetine have not been evaluated in the geriatric
112 population.

113 Pediatric — The pharmacokinetics of atomoxetine in children and adolescents are similar to
114 those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under
115 6 years of age.

116 Gender — Gender did not influence atomoxetine disposition.

117 Ethnic origin — Ethnic origin did not influence atomoxetine disposition (except that PMs are
118 more common in Caucasians).

119 **Drug-Drug Interactions**

120 CYP2D6 activity and atomoxetine plasma concentration — Atomoxetine is primarily
121 metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, inhibitors of CYP2D6
122 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed
123 in PMs. Dosage adjustment of STRATTERA in EMs may be necessary when coadministered
124 with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* Drug-Drug Interactions
125 *under* PRECAUTIONS). In vitro studies suggest that coadministration of cytochrome P450
126 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

127 Effect of atomoxetine on P450 enzymes — Atomoxetine did not cause clinically important
128 inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6,
129 and CYP2C9.

130 Albuterol — Albuterol (600 mcg iv over 2 hours) induced increases in heart rate and blood
131 pressure. These effects were potentiated by atomoxetine (60 mg BID for 5 days) and were most
132 marked after the initial coadministration of albuterol and atomoxetine (*see* Drug-Drug
133 Interactions *under* PRECAUTIONS).

134 Alcohol — Consumption of ethanol with STRATTERA did not change the intoxicating effects
135 of ethanol.

136 Desipramine — Coadministration of STRATTERA (40 or 60 mg BID for 13 days) with
137 desipramine, a model compound for CYP2D6 metabolized drugs (single dose of 50 mg), did not
138 alter the pharmacokinetics of desipramine. No dose adjustment is recommended for drugs
139 metabolized by CYP2D6.

140 Methylphenidate — Coadministration of methylphenidate with STRATTERA did not increase
141 cardiovascular effects beyond those seen with methylphenidate alone.

142 Midazolam — Coadministration of STRATTERA (60 mg BID for 12 days) with midazolam, a
143 model compound for CYP3A4 metabolized drugs (single dose of 5 mg), resulted in 15% increase
144 in AUC of midazolam. No dose adjustment is recommended for drugs metabolized by CYP3A.

145 Drugs highly bound to plasma protein — In vitro drug-displacement studies were conducted
146 with atomoxetine and other highly-bound drugs at therapeutic concentrations. Atomoxetine did
147 not affect the binding of warfarin, acetylsalicylic acid, phenytoin, or diazepam to human
148 albumin. Similarly, these compounds did not affect the binding of atomoxetine to human
149 albumin.

150 Drugs that affect gastric pH — Drugs that elevate gastric pH (magnesium hydroxide/aluminum
151 hydroxide, omeprazole) had no effect on STRATTERA bioavailability.

152 **CLINICAL STUDIES**

153 The effectiveness of STRATTERA in the treatment of ADHD was established in 6
154 randomized, double-blind, placebo-controlled studies in children, adolescents, and adults who
155 met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD (*see*
156 INDICATIONS AND USAGE).

157 **Children and Adolescents**

158 The effectiveness of STRATTERA in the treatment of ADHD was established in 4
159 randomized, double-blind, placebo-controlled studies of pediatric patients (ages 6 to 18).
160 Approximately one-third of the patients met DSM-IV criteria for inattentive subtype and
161 two-thirds met criteria for both inattentive and hyperactive/impulsive subtypes (*see*
162 INDICATIONS AND USAGE).

163 Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline
164 to endpoint for STRATTERA- and placebo-treated patients using an intent-to-treat analysis of
165 the primary outcome measure, the investigator administered and scored ADHD Rating
166 Scale-IV-Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive
167 subscales. Each item on the ADHDRS maps directly to one symptom criterion for ADHD in the
168 DSM-IV.

169 In Study 1, an 8-week randomized, double-blind, placebo-controlled, dose-response, acute
170 treatment study of children and adolescents aged 8 to 18 (N=297), patients received either a fixed
171 dose of STRATTERA (0.5, 1.2, or 1.8 mg/kg/day) or placebo. STRATTERA was administered
172 as a divided dose in the early morning and late afternoon/early evening. At the 2 higher doses,

173 improvements in ADHD symptoms were statistically significantly superior in STRATTERA-
174 treated patients compared with placebo-treated patients as measured on the ADHDRS scale. The
175 1.8-mg/kg/day STRATTERA dose did not provide any additional benefit over that observed with
176 the 1.2-mg/kg/day dose. The 0.5-mg/kg/day STRATTERA dose was not superior to placebo.

177 In Study 2, a 6-week randomized, double-blind, placebo-controlled, acute treatment study of
178 children and adolescents aged 6 to 16 (N=171), patients received either STRATTERA or
179 placebo. STRATTERA was administered as a single dose in the early morning and titrated on a
180 weight-adjusted basis according to clinical response, up to a maximum dose of 1.5 mg/kg/day.
181 The mean final dose of STRATTERA was approximately 1.3 mg/kg/day. ADHD symptoms
182 were statistically significantly improved on STRATTERA compared with placebo, as measured
183 on the ADHDRS scale. This study shows that STRATTERA is effective when administered once
184 daily in the morning.

185 In 2 identical, 9-week, acute, randomized, double-blind, placebo-controlled studies of children
186 aged 7 to 13 (Study 3, N=147; Study 4, N=144), STRATTERA and methylphenidate were
187 compared with placebo. STRATTERA was administered as a divided dose in the early morning
188 and late afternoon (after school) and titrated on a weight-adjusted basis according to clinical
189 response. The maximum recommended STRATTERA dose was 2.0 mg/kg/day. The mean final
190 dose of STRATTERA for both studies was approximately 1.6 mg/kg/day. In both studies,
191 ADHD symptoms statistically significantly improved more on STRATTERA than on placebo, as
192 measured on the ADHDRS scale.

193 Examination of population subsets based on gender and age (<12 and 12 to 17) did not reveal
194 any differential responsiveness on the basis of these subgroupings. There was not sufficient
195 exposure of ethnic groups other than Caucasian to allow exploration of differences in these
196 subgroups.

197 **Adults**

198 The effectiveness of STRATTERA in the treatment of ADHD was established in 2
199 randomized, double-blind, placebo-controlled clinical studies of adult patients, age 18 and older,
200 who met DSM-IV criteria for ADHD.

201 Signs and symptoms of ADHD were evaluated using the investigator-administered Conners
202 Adult ADHD Rating Scale Screening Version (CAARS), a 30-item scale. The primary
203 effectiveness measure was the 18-item Total ADHD Symptom score (the sum of the inattentive
204 and hyperactivity/impulsivity subscales from the CAARS) evaluated by a comparison of mean
205 change from baseline to endpoint using an intent-to-treat analysis.

206 In 2 identical, 10-week, randomized, double-blind, placebo-controlled acute treatment studies
207 (Study 5, N=280; Study 6, N=256), patients received either STRATTERA or placebo.
208 STRATTERA was administered as a divided dose in the early morning and late afternoon/early
209 evening and titrated according to clinical response in a range of 60 to 120 mg/day. The mean
210 final dose of STRATTERA for both studies was approximately 95 mg/day. In both studies,
211 ADHD symptoms were statistically significantly improved on STRATTERA, as measured on the
212 ADHD Symptom score from the CAARS scale.

213 Examination of population subsets based on gender and age (<42 and ≥42) did not reveal any
214 differential responsiveness on the basis of these subgroupings. There was not sufficient exposure
215 of ethnic groups other than Caucasian to allow exploration of differences in these subgroups.

216 **INDICATIONS AND USAGE**

217 STRATTERA is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder
218 (ADHD).

219 The effectiveness of STRATTERA in the treatment of ADHD was established in 2 placebo-
220 controlled trials in children, 2 placebo-controlled trials in children and adolescents, and 2
221 placebo-controlled trials in adults who met DSM-IV criteria for ADHD (*see* CLINICAL
222 STUDIES).

223 A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive
224 symptoms that cause impairment and that were present before age 7 years. The symptoms must
225 be persistent, must be more severe than is typically observed in individuals at a comparable level
226 of development, must cause clinically significant impairment, e.g., in social, academic, or
227 occupational functioning, and must be present in 2 or more settings, e.g., school (or work) and at
228 home. The symptoms must not be better accounted for by another mental disorder. For the
229 Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months:
230 lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to
231 follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses
232 things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least 6 of the
233 following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat,
234 inappropriate running/climbing, difficulty with quiet activities, “on the go,” excessive talking,
235 blurting answers, can’t wait turn, intrusive. For a Combined Type diagnosis, both inattentive and
236 hyperactive-impulsive criteria must be met.

237 **Special Diagnostic Considerations**

238 The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate
239 diagnosis requires the use not only of medical but also of special psychological, educational, and
240 social resources. Learning may or may not be impaired. The diagnosis must be based upon a
241 complete history and evaluation of the patient and not solely on the presence of the required
242 number of DSM-IV characteristics.

243 **Need for Comprehensive Treatment Program**

244 STRATTERA is indicated as an integral part of a total treatment program for ADHD that may
245 include other measures (psychological, educational, social) for patients with this syndrome. Drug
246 treatment may not be indicated for all patients with this syndrome. Drug treatment is not
247 intended for use in the patient who exhibits symptoms secondary to environmental factors and/or
248 other primary psychiatric disorders, including psychosis. Appropriate educational placement is
249 essential in children and adolescents with this diagnosis and psychosocial intervention is often
250 helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment
251 medication will depend upon the physician’s assessment of the chronicity and severity of the
252 patient’s symptoms.

253 **Long-Term Use**

254 The effectiveness of STRATTERA for long-term use, i.e., for more than 9 weeks in child and
255 adolescent patients and 10 weeks in adult patients, has not been systematically evaluated in
256 controlled trials. Therefore, the physician who elects to use STRATTERA for extended periods
257 should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see*
258 DOSAGE AND ADMINISTRATION).

259 **CONTRAINDICATIONS**

260 **Hypersensitivity**

261 STRATTERA is contraindicated in patients known to be hypersensitive to atomoxetine or
262 other constituents of the product (*see* WARNINGS).

263 **Monoamine Oxidase Inhibitors (MAOI)**

264 STRATTERA should not be taken with an MAOI, or within 2 weeks after discontinuing an
265 MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing
266 STRATTERA. With other drugs that affect brain monoamine concentrations, there have been
267 reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus,
268 autonomic instability with possible rapid fluctuations of vital signs, and mental status changes
269 that include extreme agitation progressing to delirium and coma) when taken in combination
270 with an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.
271 Such reactions may occur when these drugs are given concurrently or in close proximity.

272 **Narrow Angle Glaucoma**

273 In clinical trials, STRATTERA use was associated with an increased risk of mydriasis and
274 therefore its use is not recommended in patients with narrow angle glaucoma.

275 **WARNINGS**

276 **Suicidal Ideation**

277 STRATTERA increased the risk of suicidal ideation in short-term studies in children and
278 adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Pooled analyses of
279 short-term (6 to 18 weeks) placebo-controlled trials of STRATTERA in children and adolescents
280 have revealed a greater risk of suicidal ideation early during treatment in those receiving
281 STRATTERA. There were a total of 12 trials (11 in ADHD and 1 in enuresis) involving over
282 2200 patients (including 1357 patients receiving STRATTERA and 851 receiving placebo). The
283 average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients),
284 compared to none in placebo-treated patients. There was 1 suicide attempt among these
285 approximately 2200 patients, occurring in a patient treated with STRATTERA. **No suicides**
286 **occurred in these trials.** All events occurred in children 12 years of age or younger. All events
287 occurred during the first month of treatment. It is unknown whether the risk of suicidal ideation
288 in pediatric patients extends to longer-term use. A similar analysis in adult patients treated with
289 STRATTERA for either ADHD or major depressive disorder (MDD) did not reveal an increased
290 risk of suicidal ideation or behavior in association with the use of STRATTERA.

291 **All pediatric patients being treated with STRATTERA should be monitored closely for**
292 **suicidality, clinical worsening, and unusual changes in behavior, especially during the**
293 **initial few months of a course of drug therapy, or at times of dose changes. Such**
294 **monitoring would generally include at least weekly face-to-face contact with patients or**
295 **their family members or caregivers during the first 4 weeks of treatment, then every other**
296 **week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond**
297 **12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.**

298 The following symptoms have been reported with STRATTERA: anxiety, agitation, panic
299 attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor
300 restlessness), hypomania and mania. Although a causal link between the emergence of such
301 symptoms and the emergence of suicidal impulses has not been established, there is a concern
302 that such symptoms may represent precursors to emerging suicidality. Thus, patients being
303 treated with STRATTERA should be observed for the emergence of such symptoms.

304 Consideration should be given to changing the therapeutic regimen, including possibly
305 discontinuing the medication, in patients who are experiencing emergent suicidality or symptoms
306 that might be precursors to emerging suicidality, especially if these symptoms are severe or
307 abrupt in onset, or were not part of the patient's presenting symptoms.

308 Families and caregivers of pediatric patients being treated with STRATTERA should be
309 alerted about the need to monitor patients for the emergence of agitation, irritability,
310 unusual changes in behavior, and the other symptoms described above, as well as the
311 emergence of suicidality, and to report such symptoms immediately to healthcare
312 providers. Such monitoring should include daily observation by families and caregivers.

313 **Screening Patients for Bipolar Disorder** — In general, particular care should be taken in
314 treating ADHD in patients with comorbid bipolar disorder because of concern for possible
315 induction of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the
316 symptoms described above represent such a conversion is unknown. However, prior to initiating
317 treatment with STRATTERA, patients with comorbid depressive symptoms should be
318 adequately screened to determine if they are at risk for bipolar disorder; such screening should
319 include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and
320 depression.

321 **Severe Liver Injury**

322 Postmarketing reports indicate that STRATTERA can cause severe liver injury in rare
323 cases. Although no evidence of liver injury was detected in clinical trials of about 6000
324 patients, there have been two reported cases of markedly elevated hepatic enzymes and
325 bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million
326 patients during the first two years of postmarketing experience. In one patient, liver injury,
327 manifested by elevated hepatic enzymes (up to 40 X upper limit of normal (ULN)) and
328 jaundice (bilirubin up to 12 X ULN), recurred upon rechallenge, and was followed by
329 recovery upon drug discontinuation providing evidence that STRATTERA caused the liver
330 injury. Such reactions may occur several months after therapy is started, but laboratory
331 abnormalities may continue to worsen for several weeks after drug is stopped. Because of
332 probable underreporting, it is impossible to provide an accurate estimate of the true
333 incidence of these events. The patients described above recovered from their liver injury,
334 and did not require a liver transplant. However, in a small percentage of patients, severe
335 drug-related liver injury may progress to acute liver failure resulting in death or the need
336 for a liver transplant.

337 STRATTERA should be discontinued in patients with jaundice or laboratory evidence of
338 liver injury, and should not be restarted. Laboratory testing to determine liver enzyme
339 levels should be done upon the first symptom or sign of liver dysfunction (e.g., pruritus,
340 dark urine, jaundice, right upper quadrant tenderness, or unexplained “flu-like”
341 symptoms). (See also Information for Patients under PRECAUTIONS.)

342 **Serious Cardiovascular Events**

343 **Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart** 344 **Problems**

345 **Children and Adolescents** — Sudden death has been reported in association with atomoxetine
346 treatment at usual doses in children and adolescents with structural cardiac abnormalities or other
347 serious heart problems. Although some serious heart problems alone carry an increased risk of
348 sudden death, atomoxetine generally should not be used in children or adolescents with known
349 serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or
350 other serious cardiac problems that may place them at increased vulnerability to the
351 noradrenergic effects of atomoxetine.

352 **Adults** — Sudden deaths, stroke, and myocardial infarction have been reported in adults taking
353 atomoxetine at usual doses for ADHD. Although the role of atomoxetine in these adult cases is

354 also unknown, adults have a greater likelihood than children of having serious structural cardiac
355 abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or
356 other serious cardiac problems. Consideration should be given to not treating adults with
357 clinically significant cardiac abnormalities.

358 **Assessing Cardiovascular Status in Patients being Treated with Atomoxetine**

359 Children, adolescents, or adults who are being considered for treatment with atomoxetine
360 should have a careful history (including assessment for a family history of sudden death or
361 ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and
362 should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram
363 and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained
364 syncope, or other symptoms suggestive of cardiac disease during atomoxetine treatment should
365 undergo a prompt cardiac evaluation.

366 **Emergence of New Psychotic or Manic Symptoms**

367 Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or
368 mania in children and adolescents without a prior history of psychotic illness or mania can be
369 caused by atomoxetine at usual doses. If such symptoms occur, consideration should be given to
370 a possible causal role of atomoxetine, and discontinuation of treatment should be considered. In a
371 pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in
372 about 0.2% (4 patients with events out of 1939 exposed to atomoxetine for several weeks at
373 usual doses) of atomoxetine-treated patients compared to 0 out of 1056 placebo-treated patients.

374 **Allergic Events**

375 Although uncommon, allergic reactions, including angioneurotic edema, urticaria, and rash,
376 have been reported in patients taking STRATTERA.

377 **PRECAUTIONS**

378 **General**

379 Effects on blood pressure and heart rate — STRATTERA should be used with caution in
380 patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because it
381 can increase blood pressure and heart rate. Pulse and blood pressure should be measured at
382 baseline, following STRATTERA dose increases, and periodically while on therapy.

383 In pediatric placebo-controlled trials, STRATTERA-treated subjects experienced a mean
384 increase in heart rate of about 6 beats/minute compared with placebo subjects. At the final study
385 visit before drug discontinuation, 3.6% (12/335) of STRATTERA-treated subjects had heart rate
386 increases of at least 25 beats/minute and a heart rate of at least 110 beats/minute, compared with
387 0.5% (1/204) of placebo subjects. No pediatric subject had a heart rate increase of at least
388 25 beats/minute and a heart rate of at least 110 beats/minute on more than one occasion.

389 Tachycardia was identified as an adverse event for 1.5% (5/340) of these pediatric subjects
390 compared with 0.5% (1/207) of placebo subjects. The mean heart rate increase in extensive
391 metabolizer (EM) patients was 6.7 beats/minute, and in poor metabolizer (PM) patients
392 10.4 beats/minute.

393 STRATTERA-treated pediatric subjects experienced mean increases of about 1.5 mm Hg in
394 systolic and diastolic blood pressures compared with placebo. At the final study visit before drug
395 discontinuation, 6.8% (22/324) of STRATTERA-treated pediatric subjects had high systolic
396 blood pressure measurements compared with 3.0% (6/197) of placebo subjects. High systolic
397 blood pressures were measured on 2 or more occasions in 8.6% (28/324) of STRATTERA-
398 treated subjects and 3.6% (7/197) of placebo subjects. At the final study visit before drug

399 discontinuation, 2.8% (9/326) of STRATTERA-treated pediatric subjects had high diastolic
400 blood pressure measurements compared with 0.5% (1/200) of placebo subjects. High diastolic
401 blood pressures were measured on 2 or more occasions in 5.2% (17/326) of
402 STRATTERA-treated subjects and 1.5% (3/200) of placebo subjects. (High systolic and diastolic
403 blood pressure measurements were defined as those exceeding the 95th percentile, stratified by
404 age, gender, and height percentile - National High Blood Pressure Education Working Group on
405 Hypertension Control in Children and Adolescents.)

406 In adult placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase
407 in heart rate of 5 beats/minute compared with placebo subjects. Tachycardia was identified as an
408 adverse event for 3% (8/269) of these adult atomoxetine subjects compared with 0.8% (2/263) of
409 placebo subjects.

410 STRATTERA-treated adult subjects experienced mean increases in systolic (about 3 mm Hg)
411 and diastolic (about 1 mm Hg) blood pressures compared with placebo. At the final study visit
412 before drug discontinuation, 1.9% (5/258) of STRATTERA-treated adult subjects had systolic
413 blood pressure measurements ≥ 150 mm Hg compared with 1.2% (3/256) of placebo subjects. At
414 the final study visit before drug discontinuation, 0.8% (2/257) of STRATTERA-treated adult
415 subjects had diastolic blood pressure measurements ≥ 100 mm Hg compared with 0.4% (1/257)
416 of placebo subjects. No adult subject had a high systolic or diastolic blood pressure detected on
417 more than one occasion.

418 Orthostatic hypotension has been reported in subjects taking STRATTERA. In short-term,
419 child- and adolescent-controlled trials, 1.8% (6/340) of STRATTERA-treated subjects
420 experienced symptoms of postural hypotension compared with 0.5% (1/207) of placebo-treated
421 subjects. STRATTERA should be used with caution in any condition that may predispose
422 patients to hypotension.

423 Effects on urine outflow from the bladder — In adult ADHD controlled trials, the rates of
424 urinary retention (3%, 7/269) and urinary hesitation (3%, 7/269) were increased among
425 atomoxetine subjects compared with placebo subjects (0%, 0/263). Two adult atomoxetine
426 subjects and no placebo subjects discontinued from controlled clinical trials because of urinary
427 retention. A complaint of urinary retention or urinary hesitancy should be considered potentially
428 related to atomoxetine.

429 Effects on Growth — Data on the long-term effects of STRATTERA on growth come from
430 open-label studies, and weight and height changes are compared to normative population data. In
431 general, the weight and height gain of pediatric patients treated with STRATTERA lags behind
432 that predicted by normative population data for about the first 9-12 months of treatment.
433 Subsequently, weight gain rebounds and at about 3 years of treatment, patients treated with
434 STRATTERA have gained 17.9 kg on average, 0.5 kg more than predicted by their baseline data.
435 After about 12 months, gain in height stabilizes, and at 3 years, patients treated with
436 STRATTERA have gained 19.4 cm on average, 0.4 cm less than predicted by their baseline data
437 (*see* Figure 1 below).

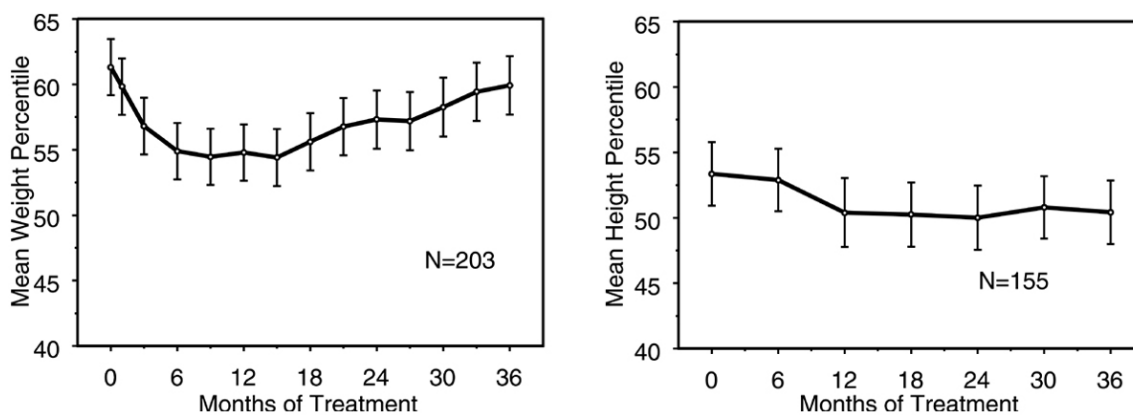


Figure 1: Mean Weight and Height Percentiles Over Time for Patients With Three Years of STRATTERA Treatment

438
439
440
441 This growth pattern was generally similar regardless of pubertal status at the time of treatment
442 initiation. Patients who were pre-pubertal at the start of treatment (girls ≤ 8 years old, boys
443 ≤ 9 years old) gained an average of 2.1 kg and 1.2 cm less than predicted after three years.
444 Patients who were pubertal (girls > 8 to ≤ 13 years old, boys > 9 to ≤ 14 years old) or late pubertal
445 (girls > 13 years old, boys > 14 years old) had average weight and height gains that were close to
446 or exceeded those predicted after three years of treatment.

447 Growth followed a similar pattern in both extensive and poor metabolizers (EMs, PMs). PMs
448 treated for at least two years gained an average of 2.4 kg and 1.1 cm less than predicted, while
449 EMs gained an average of 0.2 kg and 0.4 cm less than predicted.

450 In short-term controlled studies (up to 9 weeks), STRATTERA-treated patients lost an average
451 of 0.4 kg and gained an average of 0.9 cm, compared to a gain of 1.5 kg and 1.1 cm in the
452 placebo-treated patients. In a fixed-dose controlled trial, 1.3%, 7.1%, 19.3%, and 29.1% of
453 patients lost at least 3.5% of their body weight in the placebo, 0.5, 1.2, and 1.8 mg/kg/day dose
454 groups.

455 Growth should be monitored during treatment with STRATTERA.

456 Aggressive Behavior or Hostility — Aggressive behavior or hostility is often observed in
457 children and adolescents with ADHD, and has been reported in clinical trials and the
458 postmarketing experience of some medications indicated for the treatment of ADHD. Although
459 there is no conclusive evidence that STRATTERA causes aggressive behavior or hostility,
460 aggressive behavior or hostility was more frequently observed in clinical trials among children
461 and adolescents treated with STRATTERA compared to placebo (overall risk ratio of 1.33 - not
462 statistically significant). Patients beginning treatment for ADHD should be monitored for the
463 appearance of or worsening of aggressive behavior or hostility.

464 **Information for Patients**

465 Prescribers or other health professionals should inform patients, their families, and their
466 caregivers about the benefits and risks associated with treatment with STRATTERA and should
467 counsel them in its appropriate use. A patient Medication Guide about using STRATTERA is
468 available. The prescriber or health professional should instruct patients, their families, and their
469 caregivers to read the Medication Guide and should assist them in understanding its contents.
470 Patients should be given the opportunity to discuss the contents of the Medication Guide and to
471 obtain answers to any questions they may have. The complete text of the Medication Guide is
472 reprinted at the end of this document.

473 Patients should be advised of the following issues and asked to alert their prescriber if these
474 occur while taking STRATTERA.

475 **Suicide Risk** — Patients, their families, and their caregivers should be encouraged to be alert
476 to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility,
477 aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other
478 unusual changes in behavior, depression, and suicidal ideation, especially early during
479 STRATTERA treatment and when the dose is adjusted. Families and caregivers of patients
480 should be advised to observe for the emergence of such symptoms on a day-to-day basis, since
481 changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health
482 professional, especially if they are severe, abrupt in onset, or were not part of the patient's
483 presenting symptoms. Symptoms such as these may be associated with an increased risk for
484 suicidal thinking and behavior and indicate a need for very close monitoring and possibly
485 changes in the medication.

486 Patients initiating STRATTERA should be cautioned that liver dysfunction may develop
487 rarely. Patients should be instructed to contact their physician immediately should they develop
488 pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like"
489 symptoms.

490 Patients should be instructed to call their doctor as soon as possible should they notice an
491 increase in aggression or hostility.

492 STRATTERA is an ocular irritant. STRATTERA capsules are not intended to be opened. In
493 the event of capsule content coming in contact with the eye, the affected eye should be flushed
494 immediately with water, and medical advice obtained. Hands and any potentially contaminated
495 surfaces should be washed as soon as possible.

496 Patients should consult a physician if they are taking or plan to take any prescription or
497 over-the-counter medicines, dietary supplements, or herbal remedies.

498 Patients should consult a physician if they are nursing, pregnant, or thinking of becoming
499 pregnant while taking STRATTERA.

500 Patients may take STRATTERA with or without food.

501 If patients miss a dose, they should take it as soon as possible, but should not take more than
502 the prescribed total daily amount of STRATTERA in any 24-hour period.

503 Patients should use caution when driving a car or operating hazardous machinery until they are
504 reasonably certain that their performance is not affected by atomoxetine.

505 **Laboratory Tests**

506 Routine laboratory tests are not required.

507 **CYP2D6 metabolism** — Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and
508 a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive
509 metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are
510 available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by
511 taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of
512 some adverse effects of STRATTERA (*see* ADVERSE REACTIONS).

513 **Drug-Drug Interactions**

514 **Albuterol** — STRATTERA should be administered with caution to patients being treated with
515 systemically-administered (oral or intravenous) albuterol (or other beta₂ agonists) because the
516 action of albuterol on the cardiovascular system can be potentiated resulting in increases in heart
517 rate and blood pressure.

518 CYP2D6 inhibitors — Atomoxetine is primarily metabolized by the CYP2D6 pathway to
519 4-hydroxyatomoxetine. In EMs, selective inhibitors of CYP2D6 increase atomoxetine
520 steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage
521 adjustment of STRATTERA may be necessary when coadministered with CYP2D6 inhibitors,
522 e.g., paroxetine, fluoxetine, and quinidine (*see* DOSAGE AND ADMINISTRATION). In EM
523 individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to
524 8-fold and $C_{ss,max}$ is about 3- to 4-fold greater than atomoxetine alone.

525 In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not
526 increase the plasma concentrations of atomoxetine.

527 Monoamine oxidase inhibitors — See CONTRAINDICATIONS.

528 Pressor agents — Because of possible effects on blood pressure, STRATTERA should be used
529 cautiously with pressor agents.

530 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

531 Carcinogenesis — Atomoxetine HCl was not carcinogenic in rats and mice when given in the
532 diet for 2 years at time-weighted average doses up to 47 and 458 mg/kg/day, respectively. The
533 highest dose used in rats is approximately 8 and 5 times the maximum human dose in children
534 and adults, respectively, on a mg/m² basis. Plasma levels (AUC) of atomoxetine at this dose in
535 rats are estimated to be 1.8 times (extensive metabolizers) or 0.2 times (poor metabolizers) those
536 in humans receiving the maximum human dose. The highest dose used in mice is approximately
537 39 and 26 times the maximum human dose in children and adults, respectively, on a mg/m²
538 basis.

539 Mutagenesis — Atomoxetine HCl was negative in a battery of genotoxicity studies that
540 included a reverse point mutation assay (Ames Test), an in vitro mouse lymphoma assay, a
541 chromosomal aberration test in Chinese hamster ovary cells, an unscheduled DNA synthesis test
542 in rat hepatocytes, and an in vivo micronucleus test in mice. However, there was a slight increase
543 in the percentage of Chinese hamster ovary cells with diplochromosomes, suggesting
544 endoreduplication (numerical aberration).

545 The metabolite N-desmethyatomoxetine HCl was negative in the Ames Test, mouse
546 lymphoma assay, and unscheduled DNA synthesis test.

547 Impairment of fertility — Atomoxetine HCl did not impair fertility in rats when given in the
548 diet at doses of up to 57 mg/kg/day, which is approximately 6 times the maximum human dose
549 on a mg/m² basis.

550 **Pregnancy**

551 *Pregnancy Category C* — Pregnant rabbits were treated with up to 100 mg/kg/day of
552 atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, a
553 decrease in live fetuses and an increase in early resorptions was observed. Slight increases in the
554 incidences of atypical origin of carotid artery and absent subclavian artery were observed. These
555 findings were observed at doses that caused slight maternal toxicity. The no-effect dose for these
556 findings was 30 mg/kg/day. The 100-mg/kg dose is approximately 23 times the maximum human
557 dose on a mg/m² basis; plasma levels (AUC) of atomoxetine at this dose in rabbits are estimated
558 to be 3.3 times (extensive metabolizers) or 0.4 times (poor metabolizers) those in humans
559 receiving the maximum human dose.

560 Rats were treated with up to approximately 50 mg/kg/day of atomoxetine (approximately
561 6 times the maximum human dose on a mg/m² basis) in the diet from 2 weeks (females) or
562 10 weeks (males) prior to mating through the periods of organogenesis and lactation. In 1 of 2
563 studies, decreases in pup weight and pup survival were observed. The decreased pup survival

564 was also seen at 25 mg/kg (but not at 13 mg/kg). In a study in which rats were treated with
565 atomoxetine in the diet from 2 weeks (females) or 10 weeks (males) prior to mating throughout
566 the period of organogenesis, a decrease in fetal weight (female only) and an increase in the
567 incidence of incomplete ossification of the vertebral arch in fetuses were observed at
568 40 mg/kg/day (approximately 5 times the maximum human dose on a mg/m² basis) but not at
569 20 mg/kg/day.

570 No adverse fetal effects were seen when pregnant rats were treated with up to 150 mg/kg/day
571 (approximately 17 times the maximum human dose on a mg/m² basis) by gavage throughout the
572 period of organogenesis.

573 No adequate and well-controlled studies have been conducted in pregnant women.
574 STRATTERA should not be used during pregnancy unless the potential benefit justifies the
575 potential risk to the fetus.

576 **Labor and Delivery**

577 Parturition in rats was not affected by atomoxetine. The effect of STRATTERA on labor and
578 delivery in humans is unknown.

579 **Nursing Mothers**

580 Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if
581 atomoxetine is excreted in human milk. Caution should be exercised if STRATTERA is
582 administered to a nursing woman.

583 **Pediatric Use**

584 Anyone considering the use of STRATTERA in a child or adolescent must balance the
585 potential risks with the clinical need (*see* BOX WARNING *and* WARNINGS, Suicidal
586 Ideation).

587 The safety and efficacy of STRATTERA in pediatric patients less than 6 years of age have not
588 been established. The efficacy of STRATTERA beyond 9 weeks and safety of STRATTERA
589 beyond 1 year of treatment have not been systematically evaluated.

590 A study was conducted in young rats to evaluate the effects of atomoxetine on growth and
591 neurobehavioral and sexual development. Rats were treated with 1, 10, or 50 mg/kg/day
592 (approximately 0.2, 2, and 8 times, respectively, the maximum human dose on a mg/m² basis) of
593 atomoxetine given by gavage from the early postnatal period (Day 10 of age) through adulthood.
594 Slight delays in onset of vaginal patency (all doses) and preputial separation (10 and 50 mg/kg),
595 slight decreases in epididymal weight and sperm number (10 and 50 mg/kg), and a slight
596 decrease in corpora lutea (50 mg/kg) were seen, but there were no effects on fertility or
597 reproductive performance. A slight delay in onset of incisor eruption was seen at 50 mg/kg. A
598 slight increase in motor activity was seen on Day 15 (males at 10 and 50 mg/kg and females at
599 50 mg/kg) and on Day 30 (females at 50 mg/kg) but not on Day 60 of age. There were no effects
600 on learning and memory tests. The significance of these findings to humans is unknown.

601 **Geriatric Use**

602 The safety and efficacy of STRATTERA in geriatric patients have not been established.

603 **ADVERSE REACTIONS**

604 STRATTERA was administered to 2067 children or adolescent patients with ADHD and 270
605 adults with ADHD in clinical studies. During the ADHD clinical trials, 169 patients were treated
606 for longer than 1 year and 526 patients were treated for over 6 months.

607 The data in the following tables and text cannot be used to predict the incidence of side effects
608 in the course of usual medical practice where patient characteristics and other factors differ from

609 those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared
 610 with data obtained from other clinical investigations involving different treatments, uses, or
 611 investigators. The cited data provide the prescribing physician with some basis for estimating the
 612 relative contribution of drug and non-drug factors to the adverse event incidence in the
 613 population studied.

614 **Child and Adolescent Clinical Trials**

615 Reasons for discontinuation of treatment due to adverse events in child and adolescent clinical
 616 trials — In acute child and adolescent placebo-controlled trials, 3.5% (15/427) of atomoxetine
 617 subjects and 1.4% (4/294) placebo subjects discontinued for adverse events. For all studies,
 618 (including open-label and long-term studies), 5% of extensive metabolizer (EM) patients and 7%
 619 of poor metabolizer (PM) patients discontinued because of an adverse event. Among
 620 STRATTERA-treated patients, aggression (0.5%, N=2); irritability (0.5%, N=2); somnolence
 621 (0.5%, N=2); and vomiting (0.5%, N=2) were the reasons for discontinuation reported by more
 622 than 1 patient.

623 Commonly observed adverse events in acute child and adolescent, placebo-controlled trials —
 624 Commonly observed adverse events associated with the use of STRATTERA (incidence of 2%
 625 or greater) and not observed at an equivalent incidence among placebo-treated patients
 626 (STRATTERA incidence greater than placebo) are listed in Table 1 for the BID trials. Results
 627 were similar in the QD trial except as shown in Table 2, which shows both BID and QD results
 628 for selected adverse events. The most commonly observed adverse events in patients treated with
 629 STRATTERA (incidence of 5% or greater and at least twice the incidence in placebo patients,
 630 for either BID or QD dosing) were: dyspepsia, nausea, vomiting, fatigue, appetite decreased,
 631 dizziness, and mood swings (*see* Tables 1 and 2).
 632

633 **Table 1: Common Treatment-Emergent Adverse Events Associated with the Use of**
 634 **STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials**

Adverse Event ¹	Percentage of Patients Reporting Events from BID Trials	
	STRATTERA (N=340)	Placebo (N=207)
Gastrointestinal Disorders		
Abdominal pain upper	20	16
Constipation	3	1
Dyspepsia	4	2
Vomiting	11	9
Infections		
Ear infection	3	1
Influenza	3	1
Investigations		
Weight decreased	2	0
Metabolism and Nutritional Disorders		
Appetite decreased	14	6
Nervous System Disorders		
Dizziness (exc vertigo)	6	3
Headache	27	25

Somnolence	7	5
Psychiatric Disorders		
Crying	2	1
Irritability	8	5
Mood swings	2	0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	11	7
Rhinorrhea	4	3
Skin and Subcutaneous Tissue Disorders		
Dermatitis	4	1

635 ¹ Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events
636 did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients
637 and are possibly related to atomoxetine treatment: anorexia, blood pressure increased, early morning awakening,
638 flushing, mydriasis, sinus tachycardia, tearfulness. The following events were reported by at least 2% of patients
639 treated with atomoxetine, and equal to or less than placebo: arthralgia, gastroenteritis viral, insomnia, sore throat,
640 nasal congestion, nasopharyngitis, pruritus, sinus congestion, upper respiratory tract infection.

641

642

643

Table 2: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials

Adverse Event	Percentage of Patients Reporting Events from BID Trials		Percentage of Patients Reporting Events from QD Trials	
	STRATTERA (N=340)	Placebo (N=207)	STRATTERA (N=85)	Placebo (N=85)
Gastrointestinal Disorders				
Abdominal pain upper	20	16	16	9
Constipation	3	1	0	0
Diarrhea	3	6	4	1
Dry mouth	1	2	4	1
Dyspepsia	4	2	8	0
Nausea	7	8	12	2
Vomiting	11	9	15	1
General Disorders				
Fatigue	4	5	9	1
Psychiatric Disorders				
Mood swings	2	0	5	2

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The following adverse events occurred in at least 2% of PM patients and were either twice as frequent or statistically significantly more frequent in PM patients compared with EM patients: decreased appetite (23% of PMs, 16% of EMs); insomnia (13% of PMs, 7% of EMs); sedation (4% of PMs, 2% of EMs); depression (6% of PMs, 2% of EMs); tremor (4% of PMs, 1% of EMs); early morning awakening (3% of PMs, 1% of EMs); pruritus (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs).

651 **Adult Clinical Trials**

652 Reasons for discontinuation of treatment due to adverse events in acute adult
 653 placebo-controlled trials — In the acute adult placebo-controlled trials, 8.5% (23/270)
 654 atomoxetine subjects and 3.4% (9/266) placebo subjects discontinued for adverse events. Among
 655 STRATTERA-treated patients, insomnia (1.1%, N=3); chest pain (0.7%, N=2); palpitations
 656 (0.7%, N=2); and urinary retention (0.7%, N=2) were the reasons for discontinuation reported by
 657 more than 1 patient.

658 Commonly observed adverse events in acute adult placebo-controlled trials — Commonly
 659 observed adverse events associated with the use of STRATTERA (incidence of 2% or greater)
 660 and not observed at an equivalent incidence among placebo-treated patients (STRATTERA
 661 incidence greater than placebo) are listed in Table 3. The most commonly observed adverse
 662 events in patients treated with STRATTERA (incidence of 5% or greater and at least twice the
 663 incidence in placebo patients) were: constipation, dry mouth, nausea, appetite decreased,
 664 dizziness, insomnia, decreased libido, ejaculatory problems, impotence, urinary hesitation and/or
 665 urinary retention and/or difficulty in micturition, and dysmenorrhea (*see* Table 3).
 666

667 **Table 3: Common Treatment-Emergent Adverse Events Associated with the Use of**
 668 **STRATTERA in Acute (up to 10 weeks) Adult Trials**

Adverse Event ¹	Percentage of Patients Reporting Event	
	STRATTERA (N=269)	Placebo (N=263)
System Organ Class/Adverse Event		
Cardiac Disorders		
Palpitations	4	1
Gastrointestinal Disorders		
Constipation	10	4
Dry mouth	21	6
Dyspepsia	6	4
Flatulence	2	1
Nausea	12	5
General Disorders and Administration Site Conditions		
Fatigue and/or lethargy	7	4
Pyrexia	3	2
Rigors	3	1
Infections		
Sinusitis	6	4
Investigations		
Weight decreased	2	1
Metabolism and Nutritional Disorders		
Appetite decreased	10	3
Musculoskeletal, Connective Tissue, and Bone Disorders		
Myalgia	3	2
Nervous System Disorders		
Dizziness	6	2

Headache	17	17
Insomnia and/or middle insomnia	16	8
Paraesthesia	4	2
Sinus headache	3	1
Psychiatric Disorders		
Abnormal dreams	4	3
Libido decreased	6	2
Sleep disorder	4	2
Renal and Urinary Disorders		
Urinary hesitation and/or urinary retention and/or difficulty in micturition	8	0
Reproductive System and Breast Disorders		
Dysmenorrhea ³	7	3
Ejaculation failure ² and/or ejaculation disorder ²	5	2
Erectile disturbance ²	7	1
Impotence ²	3	0
Menses delayed ³	2	1
Menstrual disorder ³	3	2
Menstruation irregular ³	2	0
Orgasm abnormal	2	1
Prostatitis ²	3	0
Skin and Subcutaneous Tissue Disorders		
Dermatitis	2	1
Sweating increased	4	1
Vascular Disorders		
Hot flushes	3	1

669 ¹ Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events
670 did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients
671 and are possibly related to atomoxetine treatment: early morning awakening, peripheral coldness, tachycardia. The
672 following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than
673 placebo: abdominal pain upper, arthralgia, back pain, cough, diarrhea, influenza, irritability, nasopharyngitis, sore
674 throat, upper respiratory tract infection, vomiting.

675 ² Based on total number of males (STRATTERA, N=174; placebo, N=172).

676 ³ Based on total number of females (STRATTERA, N=95; placebo, N=91).

677
678 Male and female sexual dysfunction — Atomoxetine appears to impair sexual function in some
679 patients. Changes in sexual desire, sexual performance, and sexual satisfaction are not well
680 assessed in most clinical trials because they need special attention and because patients and
681 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
682 untoward sexual experience and performance cited in product labeling are likely to
683 underestimate the actual incidence. The table below displays the incidence of sexual side effects
684 reported by at least 2% of adult patients taking STRATTERA in placebo-controlled trials.

685
686

Table 4

	STRATTERA	Placebo
Erectile disturbance ¹	7%	1%
Impotence ¹	3%	0%

Orgasm abnormal	2%	1%
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687 ¹ Males only.

688
689 There are no adequate and well-controlled studies examining sexual dysfunction with
690 STRATTERA treatment. While it is difficult to know the precise risk of sexual dysfunction
691 associated with the use of STRATTERA, physicians should routinely inquire about such possible
692 side effects.

693 **Postmarketing Spontaneous Reports**

694 The following list of undesirable effects (adverse drug reactions) is based on post-marketing
695 spontaneous reports, and corresponding reporting rates have been provided.

696 **Cardiovascular system** — *Very rare (<0.01%)*: QT prolongation, syncope.

697 **Vascular disorders** — *Very rare (<0.01%)*: Peripheral vascular instability and/or Raynaud's
698 phenomenon (new onset and exacerbation of preexisting condition).

699 **DRUG ABUSE AND DEPENDENCE**

700 **Controlled Substance Class**

701 STRATTERA is not a controlled substance.

702 **Physical and Psychological Dependence**

703 In a randomized, double-blind, placebo-controlled, abuse-potential study in adults comparing
704 effects of STRATTERA and placebo, STRATTERA was not associated with a pattern of
705 response that suggested stimulant or euphoriant properties.

706 Clinical study data in over 2000 children, adolescents, and adults with ADHD and over 1200
707 adults with depression showed only isolated incidents of drug diversion or inappropriate
708 self-administration associated with STRATTERA. There was no evidence of symptom rebound
709 or adverse events suggesting a drug-discontinuation or withdrawal syndrome.

710 **Animal Experience**

711 Drug discrimination studies in rats and monkeys showed inconsistent stimulus generalization
712 between atomoxetine and cocaine.

713 **OVERDOSAGE**

714 **Human Experience**

715 There is limited clinical trial experience with STRATTERA overdose and no fatalities were
716 observed. During postmarketing, there have been reports of acute and chronic overdoses of
717 STRATTERA. No fatal overdoses of STRATTERA alone have been reported. The most
718 commonly reported symptoms accompanying acute and chronic overdoses were somnolence,
719 agitation, hyperactivity, abnormal behavior, and gastrointestinal symptoms. Signs and symptoms
720 consistent with sympathetic nervous system activation (e.g., mydriasis, tachycardia, dry mouth)
721 have also been observed.

722 **Management of Overdose**

723 An airway should be established. Monitoring of cardiac and vital signs is recommended, along
724 with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if
725 performed soon after ingestion. Activated charcoal may be useful in limiting absorption. Because
726 atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of
727 overdose.

DOSAGE AND ADMINISTRATION

728

Initial Treatment

729

730 Dosing of children and adolescents up to 70 kg body weight — STRATTERA should be
731 initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of
732 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single
733 daily dose in the morning or as evenly divided doses in the morning and late afternoon/early
734 evening. No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day (*see*
735 CLINICAL STUDIES).

736 The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg,
737 whichever is less.

738 Dosing of children and adolescents over 70 kg body weight and adults — STRATTERA
739 should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a
740 target total daily dose of approximately 80 mg administered either as a single daily dose in the
741 morning or as evenly divided doses in the morning and late afternoon/early evening. After 2 to 4
742 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not
743 achieved an optimal response. There are no data that support increased effectiveness at higher
744 doses (*see* CLINICAL STUDIES).

745 The maximum recommended total daily dose in children and adolescents over 70 kg and adults
746 is 100 mg.

Maintenance/Extended Treatment

747

748 There is no evidence available from controlled trials to indicate how long the patient with
749 ADHD should be treated with STRATTERA. It is generally agreed, however, that
750 pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the
751 physician who elects to use STRATTERA for extended periods should periodically reevaluate
752 the long-term usefulness of the drug for the individual patient.

General Dosing Information

753

754 STRATTERA may be taken with or without food.

755 The safety of single doses over 120 mg and total daily doses above 150 mg have not been
756 systematically evaluated.

757 Dosing adjustment for hepatically impaired patients — For those ADHD patients who have
758 hepatic insufficiency (HI), dosage adjustment is recommended as follows: For patients with
759 moderate HI (Child-Pugh Class B), initial and target doses should be reduced to 50% of the
760 normal dose (for patients without HI). For patients with severe HI (Child-Pugh Class C), initial
761 dose and target doses should be reduced to 25% of normal (*see* Special Populations *under*
762 CLINICAL PHARMACOLOGY).

763 Dosing adjustment for use with a strong CYP2D6 inhibitor — In children and adolescents up
764 to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and
765 quinidine, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual
766 target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is
767 well tolerated.

768 In children and adolescents over 70 kg body weight and adults administered strong CYP2D6
769 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at
770 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve
771 after 4 weeks and the initial dose is well tolerated.

772 Atomoxetine can be discontinued without being tapered.

773 **Instructions for Use/Handling**774 STRATTERA capsules are not intended to be opened, they should be taken whole. (See also
775 Information for Patients *under* PRECAUTIONS.)776 **HOW SUPPLIED**777 STRATTERA[®] (atomoxetine HCl) capsules are supplied in 10-, 18-, 25-, 40-, 60-, 80-, and
778 100-mg strengths.

779

STRATTERA [®] Capsules	10 mg*	18 mg*	25 mg*	40 mg*	60 mg*	80 mg*	100 mg*
Color	Opaque White, Opaque White	Gold, Opaque White	Opaque Blue, Opaque White	Opaque Blue, Opaque Blue	Opaque Blue, Gold	Opaque Brown, Opaque White	Opaque Brown, Opaque Brown
Identification	LILLY 3227 10 mg	LILLY 3238 18 mg	LILLY 3228 25 mg	LILLY 3229 40 mg	LILLY 3239 60 mg	LILLY 3250 80 mg	LILLY 3251 100 mg
NDC Codes:							
Bottles of 30	0002- 3227-30	0002- 3238-30	0002- 3228-30	0002- 3229-30	0002- 3239-30	0002- 3250-30	0002- 3251-30
Bottles of 1500							0002-3251- 49
Bottles of 2000	0002-3227- 07	0002- 3238-07	0002- 3228-07	0002- 3229-07	0002- 3239-07	0002-3250- 07	

780 * Atomoxetine base equivalent.

781

782 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled
783 Room Temperature].

784 Literature revised August 29, 2006

785

Medication Guide

786

STRATTERA[®]

787

Generic name: atomoxetine hydrochloride788 Read this information carefully before you start taking STRATTERA (Stra-TAIR-a) to learn
789 about the benefits and risks of STRATTERA. Read the information you get with STRATTERA
790 each time you get more STRATTERA, as there may be new information. This information does
791 not take the place of talking to your doctor about your medical condition or treatment.792 **What is the most important information I should know about STRATTERA?**793 Parents or guardians need to think about 4 important things when their child/teenager is
794 prescribed STRATTERA:

- 795
1. There is a risk of suicidal thinking
 - 796 2. How to try to prevent suicidal thoughts or actions in your child
 - 797 3. You should watch for certain signs if your child is taking STRATTERA
 - 798 4. There are benefits and risks when using STRATTERA

799 **1. There is a Risk of Suicidal Thinking**

800 Children and teenagers sometimes think about suicide, and many report trying to kill
801 themselves.

802 STRATTERA increased suicidal thinking in some children being treated for ADHD in clinical
803 trials.

804 A large study combined the results of 12 different studies of children and teenagers with
805 ADHD. In these studies, patients took either a placebo (sugar pill) or STRATTERA for 6 to
806 18 weeks. *No one committed suicide in these studies*, but some patients experienced suicidal
807 thinking. On sugar pills, no patients developed suicidal thinking. On STRATTERA, 4 out of
808 every 1000 patients developed suicidal thinking.

809 **For some children and teenagers, the risks of suicidal thinking or behaviors may be**
810 **especially high.** These include patients with

- 811 • Bipolar illness (sometimes called manic-depressive illness)
- 812 • A family history of bipolar illness
- 813 • A personal or family history of attempting suicide

814 If any of these are present, make sure you tell your healthcare provider before your child takes
815 STRATTERA.

816 **2. How to Try to Prevent Suicidal Thoughts and Actions**

817 To try to prevent suicidal thoughts and actions in your child, talk with and listen to your child
818 about his or her thoughts and feelings and pay close attention to changes in his or her moods or
819 actions, especially if the changes occur suddenly. Other important people in your child's life can
820 help by paying attention as well (e.g., brothers and sisters, teachers, and other important people).
821 The changes to look out for are listed in Section 3.

822 Whenever STRATTERA is started or its dose is changed, pay close attention to your child.
823 After starting STRATTERA, your child should generally see his or her healthcare provider:

- 824 • Once a week for the first 4 weeks
- 825 • Every 2 weeks for the next 4 weeks
- 826 • After taking STRATTERA for 12 weeks
- 827 • After 12 weeks, follow your healthcare provider's advice about how often to come back
- 828 • More often if problems or questions arise (*see* Section 3)

829 You should call your child's healthcare provider between visits if needed.

830 **3. You Should Watch for Certain Signs If Your Child is Taking STRATTERA**

831 Contact your child's healthcare provider *right away* if your child exhibits any of the following
832 signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- 833 • Thoughts about suicide or dying
- 834 • Attempts to commit suicide
- 835 • New or worse depression
- 836 • New or worse anxiety
- 837 • Feeling very agitated or restless
- 838 • Panic attacks
- 839 • Difficulty sleeping (insomnia)
- 840 • New or worse irritability
- 841 • Acting aggressive, being angry, or violent
- 842 • Acting on dangerous impulses
- 843 • An extreme increase in activity and talking
- 844 • Other unusual changes in behavior

845 **4. There are Benefits and Risks When Using STRATTERA**

846 STRATTERA is a non-stimulant medicine used to treat Attention-Deficit/Hyperactivity
847 Disorder (ADHD). In some children and teenagers who participated in clinical trials, treatment
848 with STRATTERA increased suicidal thinking. It is important to discuss all the risks of treating
849 ADHD and also the risks of not treating it. As with all treatments for ADHD, you should discuss
850 with your healthcare provider the potential benefits and risks of STRATTERA.

851 **What is STRATTERA?**

852 STRATTERA is a non-stimulant medicine used to treat ADHD in children, teenagers and
853 adults. STRATTERA contains atomoxetine hydrochloride, a selective norepinephrine reuptake
854 inhibitor. Your doctor has prescribed this medicine as part of an overall treatment plan to control
855 your symptoms of ADHD.

856 **What is ADHD?**

857 ADHD has 3 main types of symptoms: inattention, hyperactivity, and impulsiveness.
858 Symptoms of inattention include not paying attention, making careless mistakes, not listening,
859 not finishing tasks, not following directions, and being easily distracted. Symptoms of
860 hyperactivity and impulsiveness include fidgeting, talking excessively, running around at
861 inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity
862 and impulsiveness while others have more symptoms of inattentiveness. Some patients have all 3
863 types of symptoms.

864 Symptoms of ADHD in adults may include a lack of organization, problems starting tasks,
865 impulsive actions, daydreaming, daytime drowsiness, slow processing of information, difficulty
866 learning new things, irritability, lack of motivation, sensitivity to criticism, forgetfulness, low
867 self-esteem, and excessive effort to maintain some organization. The symptoms shown by adults
868 who primarily have attention problems but not hyperactivity have been commonly described as
869 Attention-Deficit Disorder (ADD).

870 Many people have symptoms like these from time to time, but patients with ADHD have these
871 symptoms more than others their age. Symptoms must be present for at least 6 months to be
872 certain of the diagnosis.

873 **Who should NOT take STRATTERA?**

874 Do not take STRATTERA if:

- 875 • you took a medicine known as a monoamine oxidase inhibitor (MAOI) in the last 2 weeks.
876 An MAOI is a medicine sometimes used for depression and other mental problems. Some
877 names of MAOI medicines are Nardil[®] (phenelzine sulfate) and Parnate[®] (tranylcypromine
878 sulfate). Taking STRATTERA with an MAOI could cause serious side effects or be
879 life-threatening.
- 880 • you have an eye disease called narrow angle glaucoma.
- 881 • you are allergic to STRATTERA or any of its ingredients. The active ingredient is
882 atomoxetine. The inactive ingredients are listed at the end of this Medication Guide.

883 **What should I tell my doctor before taking STRATTERA?**

884 Talk to your doctor before taking STRATTERA if you:

- 885 • have or had suicidal thoughts.
- 886 • have or had liver problems. You may need a lower dose.
- 887 • have high blood pressure. STRATTERA can increase blood pressure.
- 888 • have serious problems with your heart or an irregular heartbeat. STRATTERA can increase
889 heart rate (pulse).

- have low blood pressure. STRATTERA can cause dizziness or fainting in people with low blood pressure.

Tell your doctor about all the medicines you take or plan to take, including prescription and non-prescription medicines, dietary supplements, and herbal remedies. Your doctor will decide if you can take STRATTERA with your other medicines.

Certain medicines may change the way your body reacts to STRATTERA. These include medicines used to treat depression [like Paxil[®] (paroxetine hydrochloride) and Prozac[®] (fluoxetine hydrochloride)], and certain other medicines (like quinidine). Your doctor may need to change your dose of STRATTERA if you are taking it with these medicines.

STRATTERA may change the way your body reacts to oral or intravenous albuterol (or drugs with similar actions), but the effectiveness of these drugs will not be changed. Talk with your doctor before taking STRATTERA if you are taking albuterol.

How should I take STRATTERA?

- Take STRATTERA according to your doctor's instructions. This is usually taken 1 or 2 times a day (morning and late afternoon/early evening).
- You can take STRATTERA with or without food.
- If you miss a dose, take it as soon as possible, but do not take more than your total daily dose in any 24-hour period.
- Taking STRATTERA at the same time each day may help you remember.
- STRATTERA is available in several dosage strengths: 10, 18, 25, 40, 60, 80, and 100 mg.

Call your doctor right away if you take more than your prescribed dose of STRATTERA.

You should not open STRATTERA capsules, but if they are accidentally opened or broken you should avoid contact with the powder and wash away any loose powder as soon as possible with water. If any of the powder gets in your eyes you should rinse them with water immediately and contact your doctor.

Other important safety information about STRATTERA

STRATTERA can cause liver damage in rare cases. Call your doctor right away if you have itching, dark urine, yellow skin/eyes, upper right-sided abdominal tenderness, or unexplained "flu-like" symptoms.

Psychosis (abnormal thinking or hallucinations) and manic symptoms (abnormal, extreme moods, marked decreased need for sleep and/or grandiose thinking) have occurred in clinical studies of STRATTERA.

If you notice an increase in aggression or hostility since taking this medication, you should call your doctor as soon as possible.

Use caution when driving a car or operating heavy machinery until you know how STRATTERA affects you.

Talk to your doctor if you are:

- pregnant or planning to become pregnant
- breast-feeding. We do not know if STRATTERA can pass into your breast milk.

What are the common side effects of STRATTERA?

The most common side effects of STRATTERA used in teenagers and children over 6 years old are:

- upset stomach
- decreased appetite
- nausea or vomiting
- dizziness

- 936 • tiredness
- 937 • mood swings

938 Weight loss may occur after starting STRATTERA. Treatment data up to 3 years indicates
 939 minimal, if any, long-term effects of STRATTERA on weight and height. Your doctor will
 940 watch your weight and height. If you are not growing or gaining weight as expected, your doctor
 941 may change your treatment with STRATTERA.

942 The most common side effects of STRATTERA used in adults are:

- 943 • constipation
- 944 • dry mouth
- 945 • nausea
- 946 • decreased appetite
- 947 • dizziness
- 948 • problems sleeping
- 949 • sexual side effects
- 950 • problems urinating
- 951 • menstrual cramps

952 Stop taking STRATTERA and call your doctor right away if you get swelling or hives.

953 STRATTERA can cause a serious allergic reaction in rare cases.

954 This is not a complete list of side effects. Talk to your doctor if you develop any symptoms
 955 that concern you.

956 *See also* “What is the most important information I should know about STRATTERA?” *and*
 957 “Other important safety information about STRATTERA”.

958 **General advice about STRATTERA**

959 STRATTERA has not been studied in children under 6 years old.

960 Medicines are sometimes prescribed for conditions that are not mentioned in Medication
 961 Guides. Do not use STRATTERA for a condition for which it was not prescribed. Do not give
 962 STRATTERA to other people, even if they have the same symptoms you have.

963 This Medication Guide summarizes the most important information about STRATTERA. If
 964 you would like more information, talk with your doctor. You can ask your doctor or pharmacist
 965 for information on STRATTERA that is written for health professionals. You can also call
 966 1-800-Lilly-Rx (1-800-545-5979) or visit our website at www.strattera.com.

967 **What are the ingredients in STRATTERA?**

968 Active ingredient: atomoxetine.

969 Inactive ingredients: pregelatinized starch, dimethicone, gelatin, sodium lauryl sulfate, FD&C
 970 Blue No. 2, synthetic yellow iron oxide, titanium dioxide, red iron oxide, and edible black ink.

971 Store STRATTERA at room temperature.

972 *This Medication Guide has been approved by the US Food and Drug Administration.*

973 Literature revised August 29, 2006

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