

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-033**

**LABELING**

**LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules**  
**100 mg and 150 mg**

R<sub>x</sub> only

1

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Rev 0208

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**Suicidality and Antidepressant Drugs**

**Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. LUVOX CR Capsules are not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)**

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5

**DESCRIPTION**

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LUVOX® CR is an extended-release capsule for oral administration that contains fluvoxamine maleate, a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the distinct chemical series, the 2-aminoethyl oxime ethers of aralkylketones.

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Fluvoxamine maleate is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula  $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$ . Its molecular weight is 434.41.

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The structural formula is:

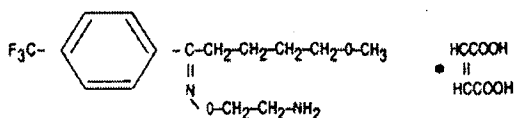
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Fluvoxamine maleate is a white to off-white, odorless, crystalline powder that is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

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LUVOX CR Capsules are available in 100 mg and 150 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each capsule contains the following inactive ingredients: talc, sugar spheres, ammonio methacrylate copolymer type B, dibutyl sebacate, red iron

25

26 oxide, FD&C Blue No. 2, titanium dioxide, gelatin (porcine- or bovine-derived), and Opacode  
27 Grey. LUVOX CR Capsules are gluten-free.

28

## 29 CLINICAL PHARMACOLOGY

### 30 Pharmacodynamics

31 The mechanism of action of fluvoxamine maleate in obsessive compulsive disorder is  
32 presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. Fluvoxamine  
33 has been shown to be a potent inhibitor of the serotonin reuptake transporter in preclinical studies,  
34 both in vitro and in vivo.

35

36 In *in vitro* studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or  
37 beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is  
38 thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal  
39 effects of some psychotropic drugs.

40

### 41 Pharmacokinetics

42 **Bioavailability:** A single-dose crossover study in 28 healthy subjects was conducted to compare  
43 the pharmacokinetics of fluvoxamine after administration of LUVOX CR Capsules and  
44 immediate-release fluvoxamine maleate tablets

45

46 In the single-dose crossover study, mean  $C_{max}$  was 38% lower and relative bioavailability  
47 was 84% for LUVOX CR Capsules versus immediate-release fluvoxamine maleate tablets.

48

49 In a multiple-dose proportionality study, LUVOX CR Capsules were administered over a dose  
50 range of 100 mg/day to 300 mg/day to 20 healthy volunteers. Steady-state plasma concentrations  
51 were achieved within a week of dosing. Mean maximum plasma concentrations were 47 ng/mL ,  
52 161 ng/mL, and 319 ng/mL, respectively, at the 100 mg, 200 mg, and 300 mg administered dose  
53 levels. Fluvoxamine exhibited nonlinear pharmacokinetics producing disproportionately higher  
54 concentrations over the dose range. The AUC and  $C_{max}$  values increased 5.7-fold following the 3-  
55 fold increase in dose from 100 mg to 300 mg.

56

57 Food caused the mean AUC and  $C_{max}$  of fluvoxamine to increase only slightly; therefore,  
58 administration of LUVOX CR Capsules with food does not significantly affect the absorption of  
59 fluvoxamine.

60

61 **Distribution/Protein Binding:** The mean apparent volume of distribution for fluvoxamine is  
62 approximately 25 L/kg, suggesting extensive tissue distribution.

63

64 Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a  
65 concentration range of 20 ng/mL to 2000 ng/mL.

66

67 **Metabolism:** Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic  
68 routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5  
69 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary  
70 excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which,  
71 together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A

72 third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%.  
 73 Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and  
 74 norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former  
 75 metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent  
 76 compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (see

77 **PRECAUTIONS – Drug Interactions.)**

78  
 79 **Elimination:** Following a <sup>14</sup>C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94%  
 80 of drug-related products was recovered in the urine within 71 hours.

81  
 82 After administration of a 100 mg, single oral dose of LUVOX CR Capsules, the mean plasma  
 83 half-life of fluvoxamine in healthy male and female volunteers was 16.3 hours.

84  
 85 **Gender:** In a study with 15 male and 13 female healthy volunteers who were administered LUVOX  
 86 CR Capsules 100 mg, AUC and C<sub>max</sub> of fluvoxamine were increased by approximately 60% in  
 87 females compared to males. There were no differences in the elimination half-life between males  
 88 and females.

89  
 90 **Elderly Subjects:** In a study using immediate-release fluvoxamine maleate tablets at 50 mg and  
 91 100 mg and comparing elderly (ages 66-73 years) and young subjects (ages 19-35 years), mean  
 92 maximum plasma concentrations in the elderly were 40% higher. The multiple-dose elimination  
 93 half-life of fluvoxamine was 17.4 hours and 25.9 hours in the elderly compared to 13.6 hours and  
 94 15.6 hours in the young subjects at steady state for 50 mg and 100 mg doses, respectively.

95  
 96 In elderly patients administered immediate-release fluvoxamine maleate tablets, the clearance of  
 97 fluvoxamine was reduced by about 50%; therefore, LUVOX CR Capsules should be slowly titrated  
 98 during initiation of therapy.

99  
 100 **Pediatric Subjects:** The pharmacokinetics of LUVOX CR Capsules have not been evaluated in  
 101 pediatric patients. However, the multiple-dose pharmacokinetics of immediate-release fluvoxamine  
 102 maleate tablets were determined in male and female children (ages 6-11 years) (Table 2) and  
 103 adolescents (ages 12-17 years) (Table 1). Steady-state plasma fluvoxamine concentrations were 2-  
 104 fold to 3-fold higher in children than in adolescents. AUC and C<sub>max</sub> in children were 1.5-fold to 2.7-  
 105 fold higher than those in adolescents (See Table 1). As in adults, both children and adolescents  
 106 exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher  
 107 AUC (0-12) and C<sub>max</sub> compared to male children; therefore, lower doses of immediate-release  
 108 fluvoxamine maleate tablets may produce therapeutic benefit (See Table 2). No gender differences  
 109 were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in  
 110 adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in  
 111 these two populations (See Table 1). Dose adjustment in adolescents (up to the adult maximum dose  
 112 of 300 mg) may be indicated to achieve therapeutic benefit.

113

**TABLE 1**

**COMPARISON OF MEAN (SD) IMMEDIATE-RELEASE TABLET FLUVOXAMINE MALEATE PHARMACOKINETIC PARAMETERS BETWEEN CHILDREN, ADOLESCENTS, AND ADULTS**

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg Twice Daily)		Dose = 300 mg/day (150 mg Twice Daily)	
	Children (n = 10)	Adolescent (n = 17)	Adolescent (n = 13)	Adult (n = 16)
AUC 0-12 (ng•h/mL/kg)	155.1 (160.9)	43.9 (27.9)	69.6 (46.6)	59.4 (40.9)
C <sub>max</sub> (ng/mL/kg)	14.8 (14.9)	4.2 (2.6)	6.7 (4.2)	5.7 (3.9)
C <sub>min</sub> (ng/mL/kg)	11.0 (11.9)	2.9 (2.0)	4.8 (3.8)	4.6 (3.2)

114

**TABLE 2**  
**COMPARISON OF MEAN (SD) IMMEDIATE-RELEASE TABLET FLUVOXAMINE MALEATE PHARMACOKINETIC PARAMETERS BETWEEN MALE AND FEMALE CHILDREN (6-11 YEARS)**

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg Twice Daily)	
	Male Children (n = 7)	Female Children (n = 3)
AUC 0-12 (ng•h/mL/kg)	95.8 (83.9)	293.5 (233.0)
C <sub>max</sub> (ng/mL/kg)	9.1 (7.6)	28.1 (21.1)
C <sub>min</sub> (ng/mL/kg)	6.6 (6.1)	21.2 (17.6)

115

116 **Hepatic and Renal Disease:** A cross-study comparison (healthy subjects versus patients with  
117 hepatic dysfunction) using immediate-release fluvoxamine maleate tablets suggested a 30%  
118 decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum  
119 plasma concentrations in renally impaired patients (creatinine clearance of 5 mL/min to 45 mL/min)  
120 after 4 weeks and 6 weeks of treatment (50 mg given twice daily, N = 13) were comparable to each  
121 other, suggesting no accumulation of fluvoxamine in these patients (see **PRECAUTIONS – Use in**  
122 **Patients with Concomitant Illness**).

123

124

### 125 Clinical Trials

126 **Social Anxiety Disorder:** The effectiveness of LUVOX CR Capsules in the treatment of social  
127 anxiety disorder was demonstrated in two 12-week, multicenter, placebo-controlled studies of  
128 adult outpatients with social anxiety disorder (DSM-IV). Patients in these trials were titrated in  
129 50 mg increments over the first six weeks of the study on the basis of response and tolerance  
130 from a dose of 100 mg/day to a fluvoxamine maleate dose within a range of 100 mg to 300 mg  
131 once-a-day.

132

133 In these studies, the effectiveness of LUVOX CR Capsules compared to placebo was  
134 evaluated on the basis of change from baseline in the Liebowitz Social Anxiety Scale (LSAS).  
135 LUVOX CR Capsules demonstrated statistically significant superiority over placebo at the  
136 primary endpoint (Week 12) as assessed by the LSAS total score in both studies.

137

138 The mean daily doses of LUVOX CR Capsules administered to patients in Study 1 and Study  
139 2 were 236 mg and 204 mg, respectively, at end of study.

140

141 Subgroup analyses generally did not indicate differences in treatment outcomes as a function  
142 of age, race, or gender.

143

144 **Obsessive Compulsive Disorder (OCD):** The effectiveness of LUVOX CR Capsules for the  
145 treatment of OCD was demonstrated in a 12-week, multicenter, placebo-controlled study of adult  
146 outpatients. Patients in this trial were titrated in 50 mg increments over the first six weeks of the  
147 study on the basis of response and tolerance from a dose of 100 mg/day to a fluvoxamine  
148 maleate dose within a range of 100 mg to 300 mg once-a-day. Patients in this study had moderate  
149 to severe OCD (DSM-IV), with mean baseline ratings on the Yale-Brown Obsessive Compulsive  
150 Scale (Y-BOCS), total scores of 26.6 and 26.3 for fluvoxamine and placebo-treatment groups,  
151 respectively.

152

153 Patients receiving LUVOX CR Capsules demonstrated statistically significant improvement  
154 over placebo patients at the primary endpoint (Week 12) compared to baseline on the Y-BOCS.  
155 The mean daily dose of LUVOX CR Capsules administered to patients was 261 mg at end of  
156 study.

157

158 Exploratory analyses for age and gender effects on outcomes did not show any significant  
159 differential responsiveness on the basis of age or sex.

160

161 The effectiveness of immediate-release fluvoxamine maleate tablets for the treatment of OCD  
162 was demonstrated in two 10-week multicenter, parallel-group studies of adult outpatients. Patients  
163 in these trials were titrated to a total daily fluvoxamine maleate dose of 150 mg/day over the first  
164 two weeks of the trial, after which the dose was adjusted within a range of 100 mg/day to 300  
165 mg/day (given in two doses per day), on the basis of response and tolerance. Patients in these  
166 studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown  
167 Obsessive Compulsive Scale (Y-BOCS) total score of 23.

168

169

170 **Pediatric OCD Study:** LUVOX CR Capsules have not been evaluated in pediatric patients.  
171 However, the effectiveness of immediate-release fluvoxamine maleate tablets for the treatment of  
172 OCD was demonstrated in a 10-week multicenter, parallel-group study in a pediatric outpatient  
173 population (children and adolescents, ages 8-17 years). Patients in this study were titrated to a total  
174 daily fluvoxamine dose of approximately 100 mg/day over the first two weeks of the trial, following  
175 which the dose was adjusted within a range of 50 mg/day to 200 mg/day (given in two doses per  
176 day) on the basis of response and tolerance. All patients had moderate-to-severe OCD (DSM-III-R)  
177 with mean baseline ratings on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)  
178 total score of 24.

179

180 Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential  
181 responsiveness on the basis of gender. Further exploratory analyses revealed a prominent treatment  
182 effect in the 8 year to 11 year age group and essentially no effect in the 12 year to 17 year age group.  
183 While the significance of these results is not clear, the 2-3 fold higher steady-state plasma  
184 fluvoxamine concentrations in children compared to adolescents (see **Pharmacokinetics**) is  
185 suggestive that decreased exposure in adolescents may have been a factor, and dose adjustment in  
186 adolescents (up to the adult maximum dose of 300 mg/day) may be indicated to achieve therapeutic  
187 benefit.

188

189 **INDICATIONS AND USAGE**

190 ***Social Anxiety Disorder:*** LUVOX CR Capsules are indicated for the treatment of social anxiety  
191 disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is  
192 characterized by a marked and persistent fear of one or more social or performance situations in  
193 which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to  
194 the feared situation almost invariably provokes anxiety, which may approach the intensity of a  
195 panic attack. The feared situations are avoided or endured with intense anxiety or distress. The  
196 avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with  
197 the person's normal routine, occupational or academic functioning, or social activities or  
198 relationships, or there is marked distress about having the phobias. Lesser degrees of  
199 performance anxiety or shyness generally do not require psychopharmacological treatment.

200

201 The efficacy of LUVOX CR Capsules was demonstrated in two 12-week trials in adult  
202 patients with social anxiety disorder (DSM-IV). LUVOX CR Capsules have not been studied in  
203 children or adolescents with social anxiety disorder (see **Clinical Trials** under **CLINICAL**  
204 **PHARMACOLOGY**):

205

206 The effectiveness of LUVOX CR Capsules in long-term treatment of social anxiety disorder,  
207 i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-  
208 controlled trials. Therefore, the health care provider who elects to prescribe LUVOX CR  
209 Capsules for extended periods should periodically re-evaluate the long-term usefulness of the  
210 drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

211

212 ***Obsessive Compulsive Disorder:*** LUVOX CR Capsules are indicated for the treatment of  
213 obsessions and compulsions in patients with obsessive compulsive disorder (OCD), as defined in  
214 the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or  
215 significantly interfere with social or occupational functioning.

216

217 The efficacy of LUVOX CR Capsules was demonstrated in one 12-week trial with obsessive  
218 compulsive outpatients with the diagnosis of OCD as defined in DSM-IV (see **Clinical Trials** under  
219 **CLINICAL PHARMACOLOGY**).

220

221 The efficacy of the immediate-release fluvoxamine maleate tablets in the treatment of OCD was  
222 demonstrated in two 10-week multicenter, parallel-group studies of adult outpatients.

223

224 Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts,  
225 impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional  
226 behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

227

228 The effectiveness of LUVOX CR Capsules for long-term use, i.e., for more than 12 weeks, has  
229 not been systematically evaluated in placebo-controlled trials. Therefore, the health care provider  
230 who elects to prescribe LUVOX CR Capsules for extended periods should periodically re-evaluate  
231 the long-term usefulness of the drug for the individual patient (see **DOSAGE AND**  
232 **ADMINISTRATION**).

233

234 **CONTRAINDICATIONS**

235 Co-administration of alosetron, tizanidine, thioridazine, or pimozide with LUVOX CR Capsules is  
 236 contraindicated (see **WARNINGS** and **PRECAUTIONS**).

237

238 The use of MAO inhibitors used in combination with LUVOX CR Capsules, or within 14 days  
 239 of discontinuing treatment with LUVOX CR Capsules is contraindicated (see **WARNINGS** and  
 240 **PRECAUTIONS**).

241

242 LUVOX CR Capsules are contraindicated in patients with a history of hypersensitivity to  
 243 fluvoxamine maleate or any of the excipients.

244

## 245 **WARNINGS**

### 246 **Clinical Worsening and Suicide Risk**

247 Patients with major depressive disorder (MDD), both adult and pediatric, may experience  
 248 worsening of their depression and/or the emergence of suicidal ideation and behavior  
 249 (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant  
 250 medications, and this risk may persist until significant remission occurs. Suicide is a known risk  
 251 of depression and certain other psychiatric disorders, and these disorders themselves are the  
 252 strongest predictors of suicide. There has been a long-standing concern, however, that  
 253 antidepressants may have a role in inducing worsening of depression and the emergence of  
 254 suicidality in certain patients during the early phases of treatment. The pooled analyses of short-  
 255 term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs  
 256 increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and  
 257 young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric  
 258 disorders. Short-term studies did not show an increase in the risk of suicidality with  
 259 antidepressants compared to placebo in adults beyond age 24; there was a reduction with  
 260 antidepressants compared to placebo in adults aged 65 and older.

261

262 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,  
 263 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-  
 264 term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-  
 265 controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-  
 266 term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients.  
 267 There was considerable variation in risk of suicidality among drugs, but a tendency toward an  
 268 increase in the younger patients for almost all drugs studied. There were differences in absolute  
 269 risk of suicidality across the different indications, with the highest incidence in MDD. The risk  
 270 differences (drug vs placebo), however, were relatively stable within age strata and across  
 271 indications. These risk differences (drug-placebo difference in the number of cases of suicidality  
 272 per 1000 patients treated) are provided in the Table 3.

273

274

275

276

**TABLE 3**  
**DRUG-PLACEBO DIFFERENCES IN NUMBER**  
**OF CASES OF SUICIDALITY PER 1000 PATIENTS TREATED**

<b>Age Range</b>	<b>Drug-Related Increases</b>
<18	14 additional cases
18-24	5 additional cases
<b>Age Range</b>	<b>Drug-Related Decreases</b>



25-64	1 fewer case
≥ 65	6 fewer cases

277  
278 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but  
279 the number was not sufficient to reach any conclusion about the drug effect on suicide.

280  
281 It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several  
282 months. However, there is substantial evidence from placebo-controlled maintenance trials in  
283 adults with depression that the use of antidepressants can delay the recurrence of depression.

284  
285 **All patients being treated with antidepressants for any indication should be monitored**  
286 **appropriately and observed closely for clinical worsening, suicidality, and unusual changes**  
287 **in behavior, especially during the initial few months of a course of drug therapy, or at times**  
288 **of dose changes, either increases or decreases**

289  
290 The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility,  
291 aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have  
292 been reported in adult and pediatric patients being treated with antidepressants for major  
293 depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.  
294 Although a causal link between the emergence of such symptoms and either the worsening of  
295 depression and/or the emergence of suicidal impulses has not been established, there is concern  
296 that such symptoms may represent precursors to emerging suicidality.

297  
298 Consideration should be given to changing the therapeutic regimen, including possibly  
299 discontinuing the medication, in patients whose depression is persistently worse, or who are  
300 experiencing emergent suicidality or symptoms that might be precursors to worsening depression  
301 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the  
302 patient's presenting symptoms.

303  
304 If the decision has been made to discontinue treatment, medication should be tapered, as  
305 rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with  
306 certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION —**  
307 **Discontinuation of Treatment with LUVOX CR Capsules**, for a description of the risks of  
308 discontinuation of LUVOX CR Capsules).

309  
310 **Families and caregivers of patients being treated with antidepressants for major**  
311 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**  
312 **alerted about the need to monitor patients for the emergence of agitation, irritability,**  
313 **unusual changes in behavior, and the other symptoms described above, as well as the**  
314 **emergence of suicidality, and to report such symptoms immediately to health care**  
315 **providers. Such monitoring should include daily observation by families and caregivers.**  
316 Prescriptions for LUVOX CR Capsules should be written for the smallest quantity of capsules  
317 consistent with good patient management, in order to reduce the risk of overdose

318  
319 **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial  
320 presentation of bipolar disorder. It is generally believed (though not established in controlled

321 trials) that treating such an episode with an antidepressant alone may increase the likelihood of  
322 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the  
323 symptoms described above represent such a conversion is unknown. However, prior to initiating  
324 treatment with an antidepressant, patients with depressive symptoms should be adequately  
325 screened to determine if they are at risk for bipolar disorder; such screening should include a  
326 detailed psychiatric history, including a family history of suicide, bipolar disorder, and  
327 depression. It should be noted that LUVOX CR Capsules is not approved for use in treating  
328 bipolar depression.

329

#### 330 **Potential for Monoamine Oxidase Inhibitors Interaction**

331 **In patients receiving another serotonin reuptake inhibitor drug in combination with**  
332 **monoamine oxidase inhibitors (MAOIs), there have been reports of serious, sometimes fatal,**  
333 **reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible**  
334 **rapid fluctuations of vital signs, and mental status changes that include extreme agitation**  
335 **progressing to delirium and coma. These reactions have also been reported in patients who**  
336 **have discontinued that drug and have been started on an MAOI. Some cases presented with**  
337 **features resembling a serotonin syndrome or neuroleptic malignant syndrome. Therefore,**  
338 **LUVOX CR Capsules should not be used in combination with an MAOI, or within 14 days of**  
339 **discontinuing treatment with an MAOI (see CONTRAINDICATIONS).**

340

#### 341 **Potential Thioridazine Interaction**

342 **The effect of fluvoxamine (25 mg immediate-release tablets given twice daily for one week) on**  
343 **thioridazine steady-state concentrations was evaluated in 10 male inpatients with**  
344 **schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine**  
345 **and sulforidazine, increased 3-fold following co-administration of fluvoxamine.**

346

347 **Thioridazine administration produces a dose-related prolongation of the QTc interval,**  
348 **which is associated with serious ventricular arrhythmias, such as torsades de pointes-type**  
349 **arrhythmias, and sudden death. It is likely that this experience underestimates the degree of**  
350 **risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine**  
351 **may be even more pronounced when it is administered at higher doses.**

352

353 **Therefore, LUVOX CR Capsules and thioridazine should not be co-administered (see**  
354 **CONTRAINDICATIONS and PRECAUTIONS).**

355

#### 356 **Potential Tizanidine Interaction**

357 **Fluvoxamine is a potent inhibitor of CYP1A2 and tizanidine is a CYP1A2 substrate. The**  
358 **effect of immediate-release fluvoxamine maleate tablets (100 mg daily for four days) on the**  
359 **pharmacokinetics and pharmacodynamics of a single dose of tizanidine has been studied in 10**  
360 **healthy male subjects. Tizanidine C<sub>max</sub> was increased approximately 12-fold (range 5-fold to**  
361 **32-fold), elimination half-life was increased by almost 3-fold, and AUC increased 33-fold**  
362 **(range 14-fold to 103-fold). The mean maximal effect on blood pressure was a 35 mm Hg**  
363 **decrease in systolic blood pressure, a 20 mm Hg decrease in diastolic blood pressure, and a 4**  
364 **beat/min decrease in heart rate. Drowsiness was significantly increased and performance on**  
365 **the psychomotor task was significantly impaired. LUVOX CR Capsules and tizanidine should**  
366 **not be used together (see CONTRAINDICATIONS and PRECAUTIONS).**

367

**368 Potential Alosetron Interaction**

369 **Fluvoxamine, an inhibitor of several CYP isozymes, has been shown to increase mean**  
370 **alosecron plasma concentrations (AUC) approximately 6-fold and prolonged the half-life by**  
371 **approximately 3-fold. Consequently, it is recommended that LUVOX CR Capsules not be**  
372 **used in combination with alosetron (see CONTRAINDICATIONS, PRECAUTIONS, and**  
373 **Lotronex™ (alosecron) package insert).**

374

**375 Use with Ramelteon**

376 Ramelteon should not be used in combination with LUVOX CR Capsules (see **PRECAUTIONS:**  
377 **Drug Interactions).**

378

**379 Potential Pimozide Interaction**

380 **Pimozide is metabolized by the CYP3A4 isozyme, and it has been demonstrated that**  
381 **ketoconazole, a potent inhibitor of CYP3A4, blocks the metabolism of this drug, resulting**  
382 **in increased plasma concentrations of parent drug. Increased plasma concentration of**  
383 **pimozide causes QT prolongation and has been associated with torsade de pointes-type**  
384 **ventricular tachycardia, sometimes fatal. As noted below, a substantial pharmacokinetic**  
385 **interaction has been observed for fluvoxamine in combination with alprazolam, a drug that**  
386 **is known to be metabolized by the CYP3A4 isozyme. Although it has not been definitively**  
387 **demonstrated that fluvoxamine is a potent CYP3A4 inhibitor, it is likely to be, given the**  
388 **substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended**  
389 **that fluvoxamine not be used in combination with pimozide (see CONTRAINDICATIONS**  
390 **and PRECAUTIONS).**

391

**392 Other Potentially Important Drug Interactions**

393 (Also see **PRECAUTIONS – Drug Interactions.**)

394

395 ***Benzodiazepines:*** Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam,  
396 triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be  
397 reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (e.g.,  
398 lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.

399

400 **Alprazolam** – When immediate-release fluvoxamine maleate tablets (100 mg given once daily)  
401 and alprazolam (1 mg given 4 times per day) were co-administered to steady state, plasma  
402 concentrations and other pharmacokinetic parameters (AUC,  $C_{max}$ ,  $T_{1/2}$ ) of alprazolam were  
403 approximately twice those observed when alprazolam was administered alone; oral clearance was  
404 reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased  
405 psychomotor performance and memory. This interaction, which has not been investigated using  
406 higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered,  
407 particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100 mg  
408 to 300 mg. If alprazolam is co-administered with LUVOX CR Capsules, the initial alprazolam  
409 dosage should be at least halved and titration to the lowest effective dose is recommended. No  
410 dosage adjustment is required for LUVOX CR Capsules.

411

412 **Diazepam** – The co-administration of LUVOX CR Capsules and diazepam is generally not  
413 advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite,  
414 N-desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species  
415 during chronic co-administration.

416  
417 Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and  
418 diazepam is derived from a study in which healthy volunteers taking 150 mg/day of immediate-  
419 release fluvoxamine maleate tablets were administered a single oral dose of 10 mg of diazepam. In  
420 these subjects (N = 8), the clearance of diazepam was reduced by 65% and that of  
421 N-desmethyldiazepam to a level that was too low to measure over the course of the two-week long  
422 study.

423  
424 It is likely that this experience significantly underestimates the degree of accumulation that  
425 might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect  
426 of fluvoxamine may even be more pronounced when it is administered at higher doses.

427  
428 Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered.

429  
430 **Mexiletine** - The effect of steady-state immediate-release fluvoxamine maleate tablets (50  
431 mg given twice daily for 7 days) on the single-dose pharmacokinetics of mexiletine (200 mg)  
432 was evaluated in 6 healthy Japanese males. The clearance of mexiletine was reduced by 38%  
433 following co-administration with fluvoxamine compared to mexiletine alone. If fluvoxamine and  
434 mexiletine are co-administered, serum mexiletine levels should be monitored.

435  
436 **Neuroleptic Malignant Syndrome (NMS) or NMS-Like Events:** Rare instances of neuroleptic  
437 malignant syndrome (NMS) or NMS-like events have been reported in association with  
438 fluvoxamine treatment when co-administered with anti-psychotics. Additionally, a small number  
439 of such cases have been reported with fluvoxamine treatment in the absence of anti-psychotic co-  
440 administration. These serious and sometimes fatal events can include hyperthermia, muscle  
441 rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status  
442 changes. As these events may result in potentially life-threatening conditions, patients receiving  
443 this combination of therapy should be monitored for the emergence of NMS-like signs and  
444 symptoms. Treatment with fluvoxamine and any concomitant anti-psychotic agent should be  
445 discontinued immediately if such events occur and supportive symptomatic treatment should be  
446 initiated.

447  
448 **Theophylline:** The effect of steady-state immediate-release fluvoxamine maleate tablets (50 mg  
449 tablets given twice daily) on the pharmacokinetics of a single dose of theophylline (375 mg as 442  
450 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of  
451 theophylline was decreased approximately 3-fold. Therefore, if theophylline is co-administered with  
452 fluvoxamine maleate, its dose should be reduced to one third of the usual daily maintenance dose  
453 and plasma concentrations of theophylline should be monitored. No dosage adjustment is required  
454 for LUVOX CR Capsules.

455  
456 **Warfarin:** When immediate-release fluvoxamine maleate tablets (50 mg given three times per day)  
457 were administered concomitantly with warfarin for two weeks, warfarin plasma concentrations

458 increased by 98% and prothrombin times were prolonged. Thus patients receiving oral  
459 anticoagulants and LUVOX CR Capsules should have their prothrombin time monitored and their  
460 anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX CR  
461 Capsules.

462  
463 **Serotonin Syndrome:** The development of a potentially life-threatening serotonin syndrome may  
464 occur with LUVOX CR Capsules treatment, particularly with concomitant use of serotonergic drugs  
465 (including triptans) and with drugs that impair metabolism of serotonin (including MAOIs).  
466 Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations,  
467 coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular  
468 aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea,  
469 vomiting, diarrhea).

470  
471 The concomitant use of LUVOX CR Capsules with MAOIs intended to treat depression is  
472 contraindicated (see **CONTRAINDICATIONS** and **WARNINGS – Potential for Interactions**  
473 **with Monoamine Oxidase Inhibitors**).

474  
475 If concomitant treatment of LUVOX CR Capsules with a 5-hydroxytryptamine receptor agonist  
476 (triptan) is clinically warranted careful observation of the patient is advised, particularly during  
477 treatment initiation and dose increase (see **PRECAUTIONS – Drug Interactions**).

478  
479 The concomitant use of fluvoxamine with serotonin precursors (such as tryptophan) is not  
480 recommended (see **PRECAUTIONS – Drug Interactions**).

481

## 482 **PRECAUTIONS**

### 483 **General**

484 **Discontinuation of Treatment with LUVOX CR Capsules:** During marketing of immediate-  
485 release fluvoxamine maleate tablets and other SSRIs and SNRIs (Serotonin and Norepinephrine  
486 Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon  
487 discontinuation of these drugs, particularly when abrupt, including the following: dysphoric  
488 mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias, such as electric  
489 shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and  
490 hypomania. While these events are generally self-limiting, there have been reports of serious  
491 discontinuation symptoms.

492

493 Patients should be monitored for these symptoms when discontinuing treatment with  
494 LUVOX CR Capsules. A gradual reduction in dose rather than abrupt cessation is recommended  
495 whenever possible. If intolerable symptoms occur following a decrease in the dose or upon  
496 discontinuation of treatment, then resuming the previously prescribed dose may be considered.  
497 Subsequently, the health care provider may continue decreasing the dose but at a more gradual  
498 rate (see **DOSAGE AND ADMINISTRATION**).

499

500

501 **Abnormal Bleeding:** SSRIs and SNRIs, including LUVOX CR Capsules, may increase the risk  
502 of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin,  
503 and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-

504 control and cohort design) have demonstrated an association between use of drugs that interfere  
505 with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related  
506 to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to  
507 life-threatening hemorrhages.

508

509 Patients should be cautioned about the risk of bleeding associated with the concomitant use of  
510 LUVOX CR Capsules and NSAIDs, aspirin, or other drugs that affect coagulation.

511

512

513 **Activation of Mania/Hypomania:** During premarketing studies of immediate-release fluvoxamine  
514 maleate tablets involving primarily depressed patients, hypomania or mania occurred in  
515 approximately 1% of patients treated with fluvoxamine. In a 10-week pediatric OCD study, 2 out of  
516 57 patients (4%) treated with fluvoxamine experienced manic reactions, compared to none of 63  
517 placebo patients. Activation of mania/hypomania has also been reported in a small proportion of  
518 patients with major affective disorder who were treated with other marketed antidepressants. As  
519 with all antidepressants, LUVOX CR Capsules should be used cautiously in patients with a history  
520 of mania.

521

522 **Seizures:** During premarketing studies with immediate-release fluvoxamine maleate tablets,  
523 seizures were reported in 0.2% of fluvoxamine-treated patients. Caution is recommended when the  
524 drug is administered to patients with a history of convulsive disorders. Fluvoxamine should be  
525 avoided in patients with unstable epilepsy and patients with controlled epilepsy should be  
526 carefully monitored. Treatment with fluvoxamine should be discontinued if seizures occur or if  
527 seizure frequency increases.

528

529 **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,  
530 including LUVOX CR Capsules. In many cases, this hyponatremia appears to be the result of the  
531 syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium  
532 lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing  
533 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise  
534 volume depleted may be at greater risk (see Geriatric Use). Discontinuation of LUVOX CR  
535 Capsules should be considered in patients with symptomatic hyponatremia and appropriate  
536 medical intervention should be instituted.

537

538 Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory  
539 impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and  
540 symptoms associated with more severe and/or acute cases have included hallucination, syncope,  
541 seizure, coma, respiratory arrest, and death.

542

543 **Use in Patients with Concomitant Illness:** Closely monitored clinical experience with immediate-  
544 release fluvoxamine maleate tablets in patients with concomitant systemic illness is limited. Caution  
545 is advised in administering LUVOX CR Capsules to patients with diseases or conditions that could  
546 affect hemodynamic responses or metabolism.

547

548 LUVOX CR Capsules or immediate-release fluvoxamine maleate tablets have not been  
549 evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction

550 or unstable heart disease. Patients with these diagnoses were systematically excluded from many  
551 clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for  
552 patients with depression or OCD who participated in premarketing studies revealed no differences  
553 between fluvoxamine and placebo in the emergence of clinically important ECG changes.

554

555 In patients with liver dysfunction, following administration of immediate-release fluvoxamine  
556 maleate tablets, fluvoxamine clearance was decreased by approximately 30%. Patients with liver  
557 dysfunction should begin with a low dose of LUVOX CR Capsules and increase it slowly with  
558 careful monitoring.

559

### 560 **Information for Patients**

561 Prescribers or other health professionals should inform patients, their families, and their  
562 caregivers about the benefits and risks associated with treatment with LUVOX CR Capsules and  
563 should counsel them in the appropriate use. A patient Medication Guide about "Antidepressant  
564 Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is  
565 available for LUVOX CR Capsules. The prescriber or health professional should instruct  
566 patients, their families, and their caregivers to read the Medication Guide and should assist them  
567 in understanding its contents. Patients should be given the opportunity to discuss the contents of  
568 the Medication Guide and to obtain answers to any questions they may have. The complete text  
569 of the Medication Guide is reprinted at the end of this document.

570

571 Patients should be advised of the following issues and asked to alert their prescriber if these  
572 occur while taking LUVOX CR Capsules.

573

574 **Abnormal Bleeding:** Patients should be cautioned about the concomitant use of fluvoxamine and  
575 NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of  
576 psychotropic drugs that interfere with serotonin reuptake and these agents has been associated  
577 with an increased risk of bleeding.

578

579 **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be  
580 encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability,  
581 hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania,  
582 other unusual changes in behavior, worsening of depression, and suicidal ideation, especially  
583 early during antidepressant treatment and when the dose is adjusted up or down. Families and  
584 caregivers of patients should be advised to look for the emergence of such symptoms on a day-  
585 to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's  
586 prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of  
587 the patient's presenting symptoms. Symptoms such as these may be associated with an increased  
588 risk for suicidal thinking and behavior and indicate the need for very close monitoring and  
589 possibly changes in the medication.

590

591 **Interference with Cognitive or Motor Performance:** Since any psychoactive drug may impair  
592 judgment, thinking, or motor skills, patients should be cautioned about operating hazardous  
593 machinery, including automobiles, until they are certain that LUVOX CR Capsules therapy does not  
594 adversely affect their ability to engage in such activities.

595

596 **Pregnancy:** Patients should be advised to notify their health care providers if they become pregnant  
597 or intend to become pregnant during therapy with LUVOX CR Capsules.

598

599 **Nursing:** Patients receiving LUVOX CR Capsules should be advised to notify their health care  
600 providers if they are breast feeding an infant (see **PRECAUTIONS – Nursing Mothers**).

601

602 **Concomitant Medication:** Patients should be advised to notify their health care providers if they are  
603 taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for  
604 clinically important interactions with LUVOX CR Capsules. Patients should be cautioned about  
605 the concomitant use of LUVOX CR Capsules and NSAIDs, aspirin, or other drugs that affect  
606 coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake  
607 and these agents has been associated with an increased risk of bleeding.

608

609 Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of  
610 LUVOX CR Capsules and triptans, tramadol or other serotonergic agents.

611

612 Because of the potential for the increased risk of serious adverse reactions, including severe  
613 lowering of blood pressure and sedation, when LUVOX CR Capsules and tizanidine are used  
614 together, fluvoxamine should not be used with tizanidine.

615

616 Because of the potential for the increased risk of serious adverse reactions when LUVOX CR  
617 Capsules and alosetron are used together, fluvoxamine should not be used with Lotronex™  
618 (alosetron).

619

620 **Alcohol:** Patients should be advised to avoid alcohol while taking LUVOX CR Capsules.

621

622 **Allergic Reactions:** Patients should be advised to notify their health care providers if they develop a  
623 rash, hives, or a related allergic phenomenon during therapy with LUVOX CR Capsules.

624

#### 625 **Laboratory Tests**

626 There are no specific laboratory tests recommended.

627

#### 628 **Drug Interactions**

629 As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

630

#### 631 **Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450**

632 **Isoenzymes:** Multiple hepatic cytochrome P450 isoenzymes are involved in the oxidative  
633 biotransformation of a large number of structurally different drugs and endogenous compounds. The  
634 available knowledge concerning the relationship of fluvoxamine and the cytochrome P450  
635 isoenzyme system has been obtained mostly from pharmacokinetic interaction studies conducted in  
636 healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of  
637 substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and  
638 also **WARNINGS** for details) and limited *in vitro* data for CYP3A4, it appears that fluvoxamine  
639 inhibits several cytochrome P450 isoenzymes that are known to be involved in the metabolism of  
640 other drugs such as: CYP1A2 (e.g. warfarin, theophylline, propranolol, tizanidine), CYP2C9 (e.g.  
641 warfarin), CYP3A4 (e.g. alprazolam), and CYP2C19 (e.g. omeprazole).



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*In vitro* data suggest that fluvoxamine is a relatively weak inhibitor of CYP2D6.

Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6 enzyme. Such individuals have been referred to as "poor metabolizers" (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an *in vivo* study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 "extensive metabolizers" (EM): mean  $C_{max}$ , AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by CYP2D6. Caution is indicated in patients known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (e.g., quinidine).

The metabolism of fluvoxamine has not been fully characterized and the effects of potent cytochrome P450 isoenzyme inhibition, such as the ketoconazole inhibition of CYP3A4, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as warfarin or theophylline, certain benzodiazepines and phenytoin. If LUVOX CR Capsules are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (see **CONTRAINDICATIONS** and **WARNINGS**).

***CNS Active Drugs:***

***Anti-psychotics:*** See **WARNINGS – Other Potentially Important Drug Interactions – Neuroleptic Malignant Syndrome (NMS) or NMS-Like Events.**

***Monoamine Oxidase Inhibitors:*** See **CONTRAINDICATIONS** and **WARNINGS.**

***Alprazolam:*** See **WARNINGS.**

***Diazepam:*** See **WARNINGS.**

***Alcohol:*** Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with immediate-release fluvoxamine maleate tablets (50 mg given twice daily) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

***Carbamazepine:*** Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of immediate-release fluvoxamine maleate tablets and carbamazepine.

***Clozapine:*** Elevated serum levels of clozapine have been reported in patients taking immediate-release fluvoxamine maleate tablets and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when

688 fluvoxamine and clozapine are co-administered. Patients should be closely monitored when  
689 LUVOX CR Capsules and clozapine are used concurrently.

690

691 **Lithium:** As with other serotonergic drugs, lithium may enhance the serotonergic effects of  
692 fluvoxamine and, therefore, the combination should be used with caution. Seizures have been  
693 reported with the co-administration of immediate-release fluvoxamine maleate tablets and lithium.

694

695 **Lorazepam:** A study of multiple doses of immediate-release fluvoxamine maleate tablets (50  
696 mg given twice daily) in healthy male volunteers (N = 12) and a single dose of lorazepam (4 mg  
697 single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone  
698 and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning;  
699 however, the co-administration of fluvoxamine and lorazepam did not produce larger mean  
700 decrements compared to lorazepam alone.

701

702 **Methadone:** Significantly increased methadone (plasma level:dose) ratios have been reported  
703 when immediate-release fluvoxamine maleate tablets were administered to patients receiving  
704 maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid  
705 withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another  
706 patient.

707

708 **Ramelteon:** When immediate-release fluvoxamine maleate tablets 100 mg twice daily was  
709 administered for 3 days prior to single-dose co-administration of ramelteon 16 mg and immediate-  
710 release fluvoxamine maleate tablets, the AUC for ramelteon increased approximately 190-fold and  
711 the C<sub>max</sub> increased approximately 70-fold compared to ramelteon administered alone. Ramelteon  
712 should not be used in combination with LUVOX CR Capsules (see **WARNINGS**).

713

714 **Serotonergic Drugs:** Based on the mechanism of action of LUVOX CR Capsules and the  
715 potential for serotonin syndrome, caution is advised when fluvoxamine is co-administered with  
716 other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an  
717 antibiotic which is a reversible non-selective MAOI), lithium, tramadol or St. John's Wort (see  
718 **WARNINGS – Serotonin Syndrome**). The concomitant use of LUVOX CR Capsules with other  
719 SSRIs, SNRIs, or tryptophan is not recommended (see **PRECAUTIONS – Drug Interactions**).

720

721 **Sumatriptan:** There have been rare postmarketing reports describing patients with weakness,  
722 hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor  
723 (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine,  
724 fluvoxamine, paroxetine, sertraline, etc.) is clinically warranted, appropriate observation of the  
725 patient is advised.

726

727 **Tacrine:** In a study of 13 healthy, male volunteers, a single 40 mg dose of tacrine added to  
728 immediate-release fluvoxamine maleate tablets 100 mg/day administered at steady state was  
729 associated with 5-fold and 8-fold increases in tacrine C<sub>max</sub> and AUC, respectively, compared to the  
730 administration of tacrine alone. Five subjects experienced nausea, vomiting, sweating, and diarrhea  
731 following co-administration, consistent with the cholinergic effects of tacrine.

732

733 **Thioridazine:** See **CONTRAINDICATIONS** and **WARNINGS**.

734

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**Triptans:** There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of fluvoxamine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS – Serotonin Syndrome**).

740

**Tizanidine:** See **CONTRAINDICATIONS** and **WARNINGS**.

741

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**Tricyclic Antidepressants (TCAs):** Significantly increased plasma TCA levels have been reported with the co-administration of immediate-release fluvoxamine maleate tablets and amitriptyline, clomipramine, or imipramine. Caution is indicated with the co-administration of LUVOX CR Capsules and TCAs; plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced.

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751

**Tryptophan:** Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of immediate-release fluvoxamine maleate tablets and tryptophan.

752

**Other Drugs:**

753

**Theophylline:** See **WARNINGS**.

754

755

**Warfarin:** See **WARNINGS**.

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**Alosetron:** Because alosetron is metabolized by a variety of hepatic CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. Fluvoxamine is a known potent inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a pharmacokinetic study, 40 healthy female subjects received fluvoxamine in escalating doses from 50 mg to 200 mg a day for 16 days, with co-administration of alosetron 1 mg on the last day. Fluvoxamine increased mean alosetron plasma concentration (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. (see **CONTRAINDICATIONS**, **PRECAUTIONS**, and Lotronex<sup>TM</sup> (alosestron) package insert).

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769

**Digoxin:** Administration of immediate-release fluvoxamine maleate tablets 100 mg daily for 18 days (N = 8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

770

**Diltiazem:** Bradycardia has been reported with the co-administration of immediate-release fluvoxamine maleate tablets and diltiazem.

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**Propranolol and Other Beta-Blockers:** Co-administration of immediate-release fluvoxamine maleate tablets 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean 5-fold increase (range 2-fold to 17-fold) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure.

779 One case of bradycardia and hypotension and a second case of orthostatic hypotension have  
780 been reported with the co-administration of immediate-release fluvoxamine maleate tablets and  
781 metoprolol.

782

783 If propranolol or metoprolol is co-administered with LUVOX CR Capsules, a reduction in the  
784 initial beta-blocker dose and more cautious dose titration are recommended. No dosage adjustment  
785 is required for LUVOX CR Capsules.

786

787 Co-administration of immediate-release fluvoxamine maleate tablets 100 mg per day with  
788 atenolol 100 mg per day (N = 6) did not affect the plasma concentrations of atenolol. Unlike  
789 propranolol and metoprolol, which undergo hepatic metabolism, atenolol is eliminated primarily by  
790 renal excretion.

791

#### 792 **Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin) –**

793 Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of  
794 the case-control and cohort design that have demonstrated an association between use of  
795 psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper  
796 gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or  
797 aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased  
798 bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients  
799 receiving warfarin therapy should be carefully monitored when LUVOX CR Capsules is initiated  
800 or discontinued.

801

802 *Effects of Smoking on Fluvoxamine Metabolism:* Smokers had a 25% increase in the metabolism  
803 of fluvoxamine compared to nonsmokers.

804

805 *Electroconvulsive Therapy (ECT):* There are no clinical studies establishing the benefits or risks of  
806 combined use of ECT and fluvoxamine maleate.

807

#### 808 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

809 *Carcinogenesis:* There was no evidence of carcinogenicity in rats treated orally with  
810 fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20  
811 months (females) or 26 months (males) . The daily doses in the high dose groups in these studies  
812 were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240  
813 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The  
814 maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m<sup>2</sup>  
815 basis.

816

817 *Mutagenesis:* No evidence of genotoxic potential was observed in a mouse micronucleus test,  
818 an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without  
819 metabolic activation.

820

821 *Impairment of Fertility:* In a study in which male and female rats were administered fluvoxamine  
822 (60 mg/kg, 120 mg/kg, or 240 mg/kg) orally prior to and during mating and gestation, fertility  
823 was impaired at doses of 120 mg/kg or greater, as evidenced by increased latency to mating,  
824 decreased sperm count, decreased epididymal weight, and decreased pregnancy rate. In addition,

825 the numbers of implantations and embryos were decreased at the highest dose. The no effect  
826 dose for fertility impairment was 60 mg/kg (approximately 2 times the maximum recommended  
827 human dose [MRHD] on a mg/m<sup>2</sup> basis).

828

### 829 **Pregnancy**

830 *Teratogenic Effects – Pregnancy Category C:* When pregnant rats were given fluvoxamine  
831 (60 mg/kg, 120 mg/kg, or 240 mg/kg) orally throughout the period of organogenesis,  
832 developmental toxicity in the form of increased embryofetal death and increased incidences of  
833 fetal eye abnormalities (folded retinas) was observed at doses of 120 mg/kg or greater.  
834 Decreased fetal body weight was seen at the high dose. The no effect dose for developmental  
835 toxicity in this study was 60 mg/kg (approximately 2 times the maximum recommended human  
836 dose [MRHD] on a mg/m<sup>2</sup> basis).

837

838 In a study in which pregnant rabbits were administered doses of up to 40 mg/kg  
839 (approximately 2 times the MRHD on a mg/m<sup>2</sup> basis) orally during organogenesis, no adverse  
840 effects on embryofetal development were observed.

841

842 In other reproductive studies in which female rats were dosed orally during pregnancy and  
843 lactation (5 mg/kg, 20 mg/kg, 80 mg/kg, or 160 mg/kg), increased pup mortality at birth was  
844 seen at doses of 80 mg/kg or greater and decreases in pup body weight and survival were  
845 observed at all doses (low effect dose approximately 0.1 times the MRHD on a mg/m<sup>2</sup> basis).

846

847 *Nonteratogenic Effects:* Neonates exposed to immediate-release fluvoxamine maleate tablets  
848 and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs) late in the third  
849 trimester have developed complications requiring prolonged hospitalization, respiratory support,  
850 and tube feeding. These findings are based on Postmarketing reports. Such complications can  
851 arise immediately upon delivery. Reported clinical findings have included respiratory distress,  
852 cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia,  
853 hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These  
854 features are consistent with either a direct toxic effect of SSRIs or SNRIs or, possibly, a drug  
855 discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent  
856 with serotonin syndrome (see **WARNINGS**).

857

858 Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary  
859 hypertension of the newborn (PPHN). PPHN is associated with substantial neonatal morbidity and  
860 mortality. In a case-control study of 377 women whose infants were born with PPHN and 836  
861 women whose infants were born healthy, the risk for developing PPHN was approximately 6-fold  
862 higher for infants exposed to SSRIs after the 20<sup>th</sup> week of gestation compared to infants who had  
863 not been exposed to antidepressants during pregnancy. PPHN occurs in 1-2 per 1000 live births in  
864 the general population.

865

866 When treating a pregnant woman with LUVOX CR Capsules during the third trimester, the  
867 physician should carefully consider both the potential risks and benefits of treatment (see  
868 **DOSAGE AND ADMINISTRATION**). Physicians should note that in a prospective  
869 longitudinal study of 201 women with a history of major depression who were euthymic at the  
870 beginning of pregnancy, women who discontinued antidepressant medication during pregnancy

871 were more likely to experience a relapse of major depression than women who continued  
872 antidepressant medication.

873

#### 874 **Labor and Delivery**

875 The effect of fluvoxamine on labor and delivery in humans is unknown.

876

#### 877 **Nursing Mothers**

878 Fluvoxamine is secreted in human breast milk. Because of the potential for serious adverse reactions  
879 in nursing infants from LUVOX CR Capsules, a decision should be made whether to discontinue  
880 nursing or discontinue the drug, taking into account the importance of the drug to the mother.

881

#### 882 **Pediatric Use**

883 LUVOX CR Capsules have not been evaluated in pediatric patients (see **BOXED WARNING**).

884 The efficacy of fluvoxamine maleate administered as immediate-release tablets for the treatment of  
885 OCD, was demonstrated in a 10-week multicenter placebo-controlled study with 120 outpatients  
886 ages 8-17. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment  
887 for up to another one to three years, equivalent to 94 patient years. The adverse event profile  
888 observed in that study was generally similar to that observed in adult studies with immediate-release  
889 fluvoxamine maleate tablets (see **ADVERSE REACTIONS** and **DOSAGE AND**  
890 **ADMINISTRATION**).

891

892 Decreased appetite and weight loss have been observed in association with the use of  
893 fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is  
894 recommended if treatment of a child with an SSRI is to be continued long term.

895

896 The risks, if any, that may be associated with fluvoxamine's extended use in children and  
897 adolescents with OCD have not been systematically assessed. The prescriber should be mindful that  
898 the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents  
899 derives from relatively short-term clinical studies and from extrapolation of experience gained with  
900 adult patients. In particular, there are no studies that directly evaluate the effects of long-term  
901 fluvoxamine use on the growth, cognitive behavioral development, and maturation of children and  
902 adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a  
903 capacity to adversely affect growth, development or maturation, the absence of such findings is not  
904 compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in  
905 chronic use (see **WARNINGS – Clinical Worsening and Suicide Risk**).

906

907 Safety and effectiveness in the pediatric population other than pediatric patients with OCD have  
908 not been established (see **BOXED WARNING** and **WARNINGS—Clinical Worsening and**  
909 **Suicide Risk**). Anyone considering the use of LUVOX CR Capsules in a child or adolescent must  
910 balance the potential risks with the clinical need.

911

#### 912 **Geriatric Use**

913

914 Approximately 230 patients and 5 patients participating in controlled premarketing studies with  
915 immediate-release fluvoxamine maleate tablets and LUVOX CR Capsules, respectively, were 65-  
916 years of age or over. No overall differences in safety were observed between these patients and  
917 younger patients. Other reported clinical experience has not identified differences in response

918 between the elderly and younger patients. However, fluvoxamine has been associated with several  
 919 cases of clinically significant hyponatremia in elderly patients (see **PRECAUTIONS –**  
 920 **General**). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly  
 921 compared to younger patients (see **Pharmacokinetics** under **CLINICAL PHARMACOLOGY**),  
 922 and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX  
 923 CR Capsules should be slowly titrated during initiation of therapy. SSRIs and SNRIs, including  
 924 LUVOX CR Capsules, have been associated with cases of clinically significant hyponatremia in  
 925 elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS,**  
 926 **Hyponatremia**).

927

928

929 **ADVERSE REACTIONS**930 **Associated with Discontinuation of Treatment**

931 Of the 279 patients with social anxiety disorder and 124 patients with OCD treated with LUVOX  
 932 CR Capsules in controlled clinical trials, 26% and 19% discontinued treatment due to an adverse  
 933 event. The most common events ( $\geq 1\%$ ) associated with discontinuation and considered to be drug  
 934 related (i.e., those events associated with dropout at a rate at least twice that of placebo) are  
 935 provided in Table 4.

936

937

938

939

**TABLE 4**  
**ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN**  
**SOCIAL ANXIETY DISORDER AND OCD POPULATIONS**

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS			
	SOCIAL ANXIETY DISORDER		OBSESSIVE COMPULSIVE DISORDER	
	LUVOX CR	PLACEBO	LUVOX CR	PLACEBO
<b>BODY AS A WHOLE</b>				
Asthenia	4	<1	2	0
Headache	3	<1	–	–
Abdominal Pain	1	0	–	–
Pain	–	–	2	0
<b>DIGESTIVE</b>				
Nausea	8	<1	6	0
Diarrhea	3	0	2	0
Anorexia <sup>1</sup>	2	0	–	–
Dyspepsia	–	–	2	0
<b>NERVOUS SYSTEM</b>				
Insomnia	5	<1	5	2
Somnolence	5	<1	4	0
Anxiety	4	<1	2	<1
Dizziness	4	0	3	0
Abnormal Thinking	2	<1	–	–
Nervousness	2	<1	–	–
Depression	1	0	–	–

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS			
	SOCIAL ANXIETY DISORDER		OBSESSIVE COMPULSIVE DISORDER	
	LUVOX CR	PLACEBO	LUVOX CR	PLACEBO
Agitation	1	0	—	—
Paresthesia	1	0	—	—
Tremor	1	0	—	—
<b>SKIN AND APPENDAGES</b>				
Sweating	1	0	—	—

940  
941 <sup>1</sup> Includes, but is not limited to, loss of appetite and decreased appetite.  
942

### 943 Incidence in Controlled Trials

944 **Commonly Observed Adverse Events:** LUVOX CR Capsules have been studied in two  
945 controlled trials of social anxiety disorder (N = 279) and one trial of OCD (N = 124). In general,  
946 adverse event rates were similar in the two data sets as well as in a study of pediatric patients with  
947 OCD treated with immediate-release fluvoxamine maleate tablets. The most commonly observed  
948 adverse events associated with the use of LUVOX CR Capsules and likely to be drug-related  
949 (incidence of 5% or greater and at least twice that for placebo) for patients in social anxiety disorder  
950 and in OCD derived from Table 5 were: *abnormal ejaculation, anorexia, anorgasmia asthenia,*  
951 *diarrhea, nausea, somnolence, sweating and tremor.* In addition, the following events occurred  
952 in the social anxiety disorder population: *dyspepsia, dizziness, insomnia, and yawning.* In the  
953 OCD population, the following additional events occurred: *accidental injury, anxiety, decreased*  
954 *libido, myalgia, pharyngitis, and vomiting.* In a study evaluating immediate-release fluvoxamine  
955 maleate tablets in pediatric patients with OCD, the following additional events were identified using  
956 the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.*  
957

958 **Adverse Events Occurring at an Incidence of 2%:** Table 5 enumerates adverse events that  
959 occurred in adults at a frequency of 2% or more, and were more frequent than in the placebo group,  
960 among patients treated with LUVOX CR Capsules in two short-term, placebo-controlled social  
961 anxiety disorder trials (12 week) and one short-term placebo-controlled OCD trial (12 week) and in  
962 which patients were dosed once-a-day in a range of 100 to 300 mg/day. This table shows the  
963 percentage of patients in each group who had at least one occurrence of an event at some time  
964 during their treatment. Reported adverse events were classified using a COSTART-based  
965 Dictionary terminology.  
966

967 The prescriber should be aware that these figures cannot be used to predict the incidence of side  
968 effects in the course of usual medical practice where patient characteristics and other factors may  
969 differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be  
970 compared with figures obtained from other clinical investigations involving different treatments,  
971 uses, and investigators. The cited figures, however, do provide the prescribing health care provider  
972 with some basis for estimating the relative contribution of drug and non-drug factors to the side-  
973 effect incidence rate in the population studied.  
974  
975

TABLE 5



976  
977  
978

**TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES  
BY BODY SYSTEM IN ADULT  
SOCIAL ANXIETY DISORDER AND OCD POPULATIONS<sup>1</sup>**

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS REPORTING EVENT			
	SOCIAL ANXIETY DISORDER		OBSESSIVE COMPULSIVE DISORDER	
	LUVOX CR N = 279	PLACEBO N = 276	LUVOX CR N = 124	PLACEBO N = 124
<b>BODY AS A WHOLE</b>				
Headache	35	30	32	31
Asthenia	24	10	26	8
Pain <sup>2</sup>	—	—	10	8
Abdominal Pain	5	4	—	—
Accidental Injury	—	—	5	3
Chest Pain	3	1	—	—
Viral Infection	—	—	2	<1
<b>CARDIOVASCULAR</b>				
Palpitation	3	1	—	—
Vasodilatation	2	<1	—	—
Hypertension	—	—	2	<1
<b>DIGESTIVE SYSTEM</b>				
Nausea	39	11	34	13
Diarrhea	14	5	18	8
Anorexia <sup>3</sup>	14	1	13	5
Dyspepsia	10	4	8	5
Constipation	6	5	4	<1
Vomiting	—	—	6	2
Tooth Disorder	—	—	2	<1
Liver Function Test Abnormal	2	<1	—	—
Gingivitis	—	—	2	0
<b>HEMIC AND LYMPHATIC</b>				
Ecchymosis	—	—	4	2
<b>METABOLIC AND NUTRITIONAL DISORDERS</b>				
Weight Loss	—	—	2	<1
<b>MUSCULOSKELETAL</b>				
Myalgia	—	—	5	2
<b>NERVOUS SYSTEM</b>				
Insomnia	32	13	35	20
Somnolence	26	9	27	11
Dizziness	15	7	12	10
Dry Mouth	11	8	10	9
Nervousness	10	9	—	—
Libido Decreased	6	4	6	2
Male	8	6	10	5
Female	4	3	4	1
Anxiety	8	5	6	2
Tremor	8	<1	6	0
Abnormal Thinking	3	2	3	<1
Abnormal Dreams	3	2	—	—
Agitation	3	<1	2	<1

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS REPORTING EVENT			
	SOCIAL ANXIETY DISORDER		OBSESSIVE COMPULSIVE DISORDER	
	LUVOX CR N = 279	PLACEBO N = 276	LUVOX CR N = 124	PLACEBO N = 124
Hypertonia	2	1	–	–
Apathy	–	–	3	0
Paresthesia	3	2	–	–
Neurosis	–	–	2	<1
Twitching	–	–	2	0
<b>RESPIRATORY SYSTEM</b>				
Pharyngitis	–	–	6	<1
Yawn	5	<1	2	0
Laryngitis	–	–	3	0
Bronchitis	2	1	–	–
Epistaxis	–	–	2	0
<b>SKIN</b>				
Sweating	6	2	7	<1
Acne	–	–	2	0
<b>SPECIAL SENSES</b>				
Taste Perversion	2	<1	2	<1
Amblyopia	–	–	2	<1
<b>UROGENITAL</b>				
Abnormal Ejaculation	11	2	10	0
Anorgasmia	5	1	5	0
Male	4	2	4	0
Female	5	0	5	0
Menorrhagia	–	–	3	0
Sexual Function Abnormal	3	<1	2	<1
Male	2	1	4	3
Female	3	0	0	0
Urinary Tract Infection	2	<1	–	–
Polyuria	–	–	2	<1

979

980 <sup>1</sup> Events for which fluvoxamine maleate incidence was equal to or less than placebo include the  
981 following for social anxiety disorder patients: abdominal pain, accidental injury, back pain, flu  
982 syndrome, infection, pain, flatulence, pharyngitis, rhinitis, rash, and dysmenorrhea. In OCD  
983 patients the following events were seen: abdominal pain, flu syndrome, infection, palpitation,  
984 flatulence, increased appetite, weight gain, abnormal dreams, amnesia, hypertonia, nervousness,  
985 paresthesia, increased cough, dyspnea, rhinitis, and ear pain.

986 <sup>2</sup> Term includes body aches/pains, dental pain, pain from surgery, unspecified pain, and general  
987 pain secondary to injuries (sprains, fractures).

988 <sup>3</sup> Includes, but is not limited to, loss of appetite and decreased appetite.  
989

#### 990 Other Adverse Events in OCD Pediatric Population

991 In pediatric patients (N = 57) treated with immediate-release fluvoxamine maleate tablets, the  
992 overall profile of adverse events was generally similar to that seen in adult studies, as shown in  
993 Table 5. However, the following adverse events, not appearing in Table 5, were reported in two  
994 or more of the pediatric patients and were more frequent with immediate-release fluvoxamine

995 maleate tablets than with placebo: cough increase, dysmenorrhea, emotional lability, fever,  
996 flatulence, flu syndrome, hyperkinesia, infection, manic reaction, rash, rhinitis, and sinusitis.

997

#### 998 **Male and Female Sexual Dysfunction with SSRIs**

999 Although changes in sexual desire, sexual performance and sexual satisfaction often occur as  
1000 manifestations of a psychiatric disorder and with aging, they may also be a consequence of  
1001 pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake  
1002 inhibitors (SSRIs) can cause such untoward sexual experiences.

1003

1004 Reliable estimates of the incidence and severity of untoward experiences involving sexual  
1005 desire, performance and satisfaction are difficult to obtain, however, in part because patients and  
1006 health care providers may be reluctant to discuss them. Accordingly, estimates of the incidence  
1007 of untoward sexual experience and performance cited in product labeling are likely to  
1008 underestimate their actual incidence.

1009

1010 Table 6 displays the incidence of sexual side effects reported by at least 2% of patients taking  
1011 LUVOX CR capsules in placebo-controlled trials of social anxiety disorder and OCD.

1012

1013

1014 **TABLE 6**  
1015 **PERCENTAGE OF PATIENTS REPORTING SEXUAL ADVERSE EVENTS IN**  
**PLACEBO-CONTROLLED TRIALS**

	<b>LUVOX CR</b> <b>N=403</b>	<b>Placebo</b> <b>N=400</b>
Abnormal Ejaculation	11	2
Anorgasmia		
Male	4	1
Female	5	0
Impotence	2	3
Libido Decreased		
Male	8	5
Female	4	2
Sexual Function Abnormal		
Male	3	5
Female	2	0

1016

1017 Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a  
1018 known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

1019

1020 While it is difficult to know the precise risk of sexual dysfunction associated with the use of  
1021 SSRIs, health care providers should routinely inquire about such possible side effects.

1022

#### 1023 **Weight and Vital Sign Changes**

1024 No statistically significant differences in weight gain or loss were found between patients treated  
1025 with LUVOX CR Capsules or placebo. Comparisons of immediate-release fluvoxamine maleate  
1026 tablets or LUVOX CR Capsules versus placebo groups in separate short-term trials on (1) median  
1027 change from baseline on various vital signs variables and on (2) incidence of patients meeting

1028 criteria for potentially important changes from baseline on various measures of vital signs variables  
1029 revealed no important differences between fluvoxamine maleate and placebo.

1030

#### 1031 **Laboratory Changes**

1032 Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX CR Capsules versus  
1033 placebo groups in separate short-term trials on (1) median change from baseline on various serum  
1034 chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for  
1035 potentially important changes from baseline on various serum chemistry, hematology, and  
1036 urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

1037

#### 1038 **ECG Changes**

1039 Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX CR Capsules and  
1040 placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from  
1041 baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially  
1042 important changes from baseline on various ECG variables revealed no important differences  
1043 between fluvoxamine maleate and placebo.

1044

#### 1045 **Other Events Observed During the Premarketing Evaluation of Fluvoxamine**

1046 During premarketing clinical trials conducted in North America and Europe, multiple doses of  
1047 immediate-release fluvoxamine maleate tablets were administered for a combined total of 2737  
1048 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events  
1049 associated with this exposure were recorded by clinical investigators using descriptive terminology  
1050 of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the  
1051 proportion of individuals experiencing adverse events without first grouping similar types of  
1052 untoward events into a limited (i.e., reduced) number of standard event categories.

1053

1054 In the tabulations which follow, a COSTART-based Dictionary terminology has been used to  
1055 classify reported adverse events. If the COSTART term for an event was so general as to be  
1056 uninformative, it was replaced with a more informative term. The frequencies presented, therefore,  
1057 represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate  
1058 who experienced an event of the type cited on at least one occasion while receiving fluvoxamine  
1059 maleate. All reported events are included in the list below, with the following exceptions: 1) those  
1060 events already listed in Table 2, which tabulates incidence rates of common adverse experiences in  
1061 placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a  
1062 drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex,  
1063 herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which  
1064 were reported in only one patient and judged to not be potentially serious are not included. It is  
1065 important to emphasize that, although the events reported did occur during treatment with  
1066 fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

1067

1068 Events are further classified within body system categories and enumerated in order of  
1069 decreasing frequency using the following definitions: frequent adverse events are defined as those  
1070 occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those  
1071 occurring between 1/100 and 1/1000 patients; and rare adverse events are those occurring in less  
1072 than 1/1000 patients.

1073

1074 **Body as a Whole: Frequent:** malaise; **Infrequent:** allergic reaction, neck pain, neck rigidity,  
1075 overdose, photosensitivity reaction, suicide attempt; **Rare:** cyst, pelvic pain, sudden death.

1076

1077 **Cardiovascular System: Frequent:** hypertension, hypotension, syncope; **Infrequent:** angina  
1078 pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay,  
1079 heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; **Rare:** AV block,  
1080 cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary  
1081 infarction, supraventricular extrasystoles.

1082

1083 **Digestive System: Frequent:** elevated liver transaminases; **Infrequent:** colitis, eructation,  
1084 esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, glossitis,  
1085 hemorrhoids, melena, rectal hemorrhage, stomatitis; **Rare:** biliary pain, cholecystitis, cholelithiasis,  
1086 fecal incontinence, hematemesis, intestinal obstruction, jaundice.

1087

1088 **Endocrine System: Infrequent:** hypothyroidism; **Rare:** goiter.

1089

1090 **Hemic and Lymphatic Systems: Infrequent:** anemia, leukocytosis, lymphadenopathy,  
1091 thrombocytopenia; **Rare:** leukopenia, purpura.

1092

1093 **Metabolic and Nutritional Systems: Frequent:** edema, weight gain; **Infrequent:** dehydration,  
1094 hypercholesterolemia; **Rare:** diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia,  
1095 hypokalemia, lactate dehydrogenase increased.

1096

1097 **Musculoskeletal System: Infrequent:** arthralgia, arthritis, bursitis, generalized muscle spasm,  
1098 myasthenia, tendinous contracture, tenosynovitis; **Rare:** arthrosis, myopathy, pathological fracture.

1099

1100 **Nervous System: Frequent:** amnesia, apathy, hyperkinesia, hypokinesia, manic reaction,  
1101 myoclonus, psychotic reaction; **Infrequent:** agoraphobia, akathisia, ataxia, CNS depression,  
1102 convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional  
1103 lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility,  
1104 hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased  
1105 libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching,  
1106 vertigo; **Rare:** akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech,  
1107 tardive dyskinesia, torticollis, trismus, withdrawal syndrome.

1108

1109 **Respiratory System: Frequent:** cough increased, sinusitis; **Infrequent:** asthma, bronchitis,  
1110 hoarseness, hyperventilation; **Rare:** apnea, congestion of upper airway, hemoptysis, hiccups,  
1111 laryngismus, obstructive pulmonary disease, pneumonia.

1112

1113 **Skin: Infrequent:** alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin  
1114 discoloration, urticaria.

1115

1116 **Special Senses: Infrequent:** accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes,  
1117 ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect;  
1118 **Rare:** corneal ulcer, retinal detachment.

1119

1120 **Urogenital System: Infrequent:** anuria, breast pain, cystitis, delayed menstruation<sup>1</sup>, dysuria, female  
 1121 lactation<sup>1</sup>, hematuria, menopause<sup>1</sup>, metrorrhagia<sup>1</sup>, nocturia, premenstrual syndrome<sup>1</sup>, urinary  
 1122 incontinence, urinary urgency, urination impaired, vaginal hemorrhage<sup>1</sup>, vaginitis<sup>1</sup>; **Rare:** kidney  
 1123 calculus, hematospermia<sup>2</sup>, oliguria.

1124

1125 <sup>1</sup> Based on the number of females.

1126 <sup>2</sup> Based on the number of males.

1127

## 1128 **Postmarketing Reports**

1129 Voluntary reports of adverse events in patients taking fluvoxamine maleate immediate-release  
 1130 tablets that have been received since market introduction and are of unknown causal relationship to  
 1131 fluvoxamine use include: acute renal failure, agranulocytosis, amenorrhea, anaphylactic reaction,  
 1132 angioedema, aplastic anemia, bullous eruption, Henoch-Schoenlein purpura, hepatitis,  
 1133 hyponatremia, ileus, laryngismus, neuropathy, pancreatitis, porphyria, priapism, serotonin  
 1134 syndrome, severe akinesia with fever when fluvoxamine was co-administered with antipsychotic  
 1135 medication, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, and ventricular  
 1136 tachycardia (including torsades de pointes) .

1137

## 1138 **DRUG ABUSE AND DEPENDENCE**

### 1139 **Controlled Substance Class**

1140 LUVOX CR is not a controlled substance.

1141

### 1142 **Physical and Psychological Dependence**

1143 The potential for abuse, tolerance and physical dependence with immediate release fluvoxamine  
 1144 maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena  
 1145 was found. The discontinuation effects of LUVOX CR Capsules were not systematically evaluated  
 1146 in controlled clinical trials. LUVOX CR Capsules were not systematically studied in clinical trials  
 1147 for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It  
 1148 should be noted, however, that patients at risk for drug dependency were systematically excluded  
 1149 from investigational studies of immediate-release fluvoxamine maleate. Generally, it is not possible  
 1150 to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS  
 1151 active drug will be misused, diverted, and/or abused once marketed. Consequently, health care  
 1152 providers should carefully evaluate patients for a history of drug abuse and follow such patients  
 1153 closely, observing them for signs of LUVOX CR misuse or abuse (i.e., development of tolerance,  
 1154 incrementation of dose, drug-seeking behavior).

1155

## 1156 **OVERDOSAGE**

### 1157 **Human Experience**

1158 Exposure to immediate-release fluvoxamine maleate tablets includes over 45,000 patients treated in  
 1159 clinical trials and an estimated exposure of 50,000,000 patients treated during worldwide marketing  
 1160 experience (end of 2005). Of the 539 cases of deliberate or accidental overdose involving  
 1161 fluvoxamine reported from this population, there were 55 deaths. Of these, 9 were in patients  
 1162 thought to be taking immediate-release fluvoxamine tablets alone and the remaining 46 were in  
 1163 patients taking fluvoxamine along with other drugs. Among non-fatal overdose cases, 404 patients  
 1164 recovered completely. Five patients experienced adverse sequelae of overdosage, to include  
 1165 persistent mydriasis, unsteady gait, hypoxic encephalopathy, kidney complications (from trauma  
 1166 associated with overdose), bowel infarction requiring a hemicolectomy, and vegetative state. In 13

1167 patients, the outcome was provided as abating at the time of reporting. In the remaining 62 patients,  
1168 the outcome was unknown. The largest known ingestion of fluvoxamine immediate-release tablets  
1169 involved 12,000 mg (equivalent to 2 to 3 months' dosage). The patient fully recovered. However,  
1170 ingestions as low as 1,400 mg have been associated with lethal outcome, indicating considerable  
1171 prognostic variability.

1172

1173 In the controlled clinical trials with 403 patients treated with LUVOX CR Capsules, there was one  
1174 nonfatal intentional overdose.

1175

1176 Commonly ( $\geq 5\%$ ) observed adverse events associated with fluvoxamine maleate overdose  
1177 include gastrointestinal complaints (nausea, vomiting, and diarrhea), coma, hypokalemia,  
1178 hypotension, respiratory difficulties, somnolence, and tachycardia. Other notable signs and  
1179 symptoms seen with immediate-release fluvoxamine maleate overdose (single or multiple drugs)  
1180 include bradycardia, ECG abnormalities, (such as heart arrest, QT interval prolongation, first  
1181 degree atrioventricular block, bundle branch block, and junctional rhythm), convulsions,  
1182 dizziness, liver function disturbances, tremor, and increased reflexes.

1183

#### 1184 **Management of Overdose**

1185 Treatment should consist of those general measures employed in the management of overdosage  
1186 with any antidepressant.

1187

1188 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital  
1189 signs. General supportive and symptomatic measures are also recommended. Induction of emesis  
1190 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway  
1191 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic  
1192 patients.

1193

1194 Activated charcoal should be administered. Due to the large volume of distribution of this  
1195 drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of  
1196 benefit. No specific antidotes for fluvoxamine are known.

1197

1198 A specific caution involves patients taking, or recently having taken, fluvoxamine maleate  
1199 who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation  
1200 of the parent tricyclic and/or an active metabolite may increase the possibility of clinically  
1201 significant sequelae and extend the time needed for close medical observation (see *Tricyclic*  
1202 *Antidepressants (TCAs)* under **PRECAUTIONS**).

1203

1204 In managing overdosage, consider the possibility of multiple drug involvement. The health  
1205 care provider should consider contacting a poison control center for additional information on  
1206 the treatment of any overdose. Telephone numbers for certified poison control centers are listed  
1207 in the *Physicians' Desk Reference* (PDR).

1208

#### 1209 **DOSAGE AND ADMINISTRATION**

##### 1210 **Social anxiety disorder and OCD**

1211 The recommended starting dose for LUVOX CR Capsules in adult patients is 100 mg once per day.  
1212 LUVOX CR Capsules should be administered, with or without food, as a single daily dose at

1213 bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX CR Capsules in  
1214 social anxiety disorder and OCD, patients were titrated in 50 mg increments within a dose range of  
1215 100 mg/day to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every  
1216 week, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day.

1217

1218 Capsules should not be crushed or chewed.

1219

## 1220 **Special Populations**

### 1221 **Dosage for Elderly or Hepatically Impaired Patients**

1222 Elderly patients and those with hepatic impairment have been observed to have a decreased  
1223 clearance of fluvoxamine maleate. Consequently, it may be appropriate to titrate slowly following  
1224 the initial dose of 100 mg in these patient groups.

1225

### 1226 *Treatment of Pregnant Women During the Third Trimester*

1227 No neonates have been exposed to LUVOX CR Capsules. Neonates exposed to immediate-  
1228 release fluvoxamine maleate tablets and other SSRIs or SNRIs late in the third trimester have  
1229 developed complications requiring prolonged hospitalization, respiratory support, and tube  
1230 feeding (see **PRECAUTIONS**). When treating pregnant women with LUVOX CR Capsules  
1231 during the third trimester, the health care provider should carefully consider the potential risks  
1232 and benefits of treatment. The health care provider may consider tapering LUVOX CR Capsules  
1233 in the third trimester.

1234

### 1235 **Maintenance/Continuation of Extended Treatment**

1236 Although the efficacy of LUVOX CR Capsules beyond 12 weeks of dosing for social anxiety  
1237 disorder and OCD has not been documented in controlled trials, social anxiety disorder and OCD  
1238 are chronic conditions, and it is reasonable to consider continuation for a responding patient. Dosage  
1239 adjustments should be made to maintain the patient on the lowest effective dosage, and patients  
1240 should be periodically reassessed to determine the need for continued treatment.

1241

### 1242 **Switching Patients To or From a Monoamine Oxidase Inhibitor:**

1243 At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with  
1244 LUVOX CR Capsules. Similarly, at least 14 days should be allowed after stopping LUVOX CR  
1245 Capsules before starting an MAOI.

1246


### 1247 **Discontinuation of Treatment with LUVOX CR Capsules**

1248 Symptoms associated with discontinuation of other SSRIs or SNRIs have been reported (see  
1249 **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing  
1250 treatment. A gradual reduction in the dose rather than abrupt cessation is recommended  
1251 whenever possible. If intolerable symptoms occur following a decrease in the dose or upon  
1252 discontinuation of treatment, then resuming the previously prescribed dose may be considered.  
1253 Subsequently, the health care provider may continue decreasing the dose but at a more gradual  
1254 rate.

1255


## 1256 **HOW SUPPLIED**



1257 **100 mg Extended-Release Capsules:** Available in a two-piece gelatin capsule (dark blue  
 1258 opaque cap/white opaque body) imprinted with  on one side of the cap and LCR 100 on the  
 1259 other side of the cap.

1260 Bottles of 30..... NDC 68727-600-01

1261

1262 **150 mg Extended-Release Capsules:** Available in a two-piece gelatin capsule (dark blue  
 1263 opaque cap/powder blue opaque body) imprinted with  on one side of the cap and LCR 150  
 1264 on the other side of the cap.

1265 Bottles of 30..... NDC 68727-601-01

1266

1267 Storage

1268 LUVOX CR Capsules should be protected from high humidity and stored at 25°C (77°F);  
 1269 excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

1270 Avoid exposure to temperatures above 30°C (86°F).

1271

1272 Dispense in tight containers.

1273

1274 **Keep out of reach of children.**

1275 Lotronex™ is a trademark of GlaxoSmithKline

1276 LUVOX® is a registered trademark of Solvay Pharmaceuticals, Inc.

1277

1278 Distributed by:

1279

1280 **Jazz Pharmaceuticals, Inc.**

1281 Palo Alto, CA 94304

1282

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## Medication Guide

1289

### Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

1290

1291

1292 Read the Medication Guide that comes with your or your family member's antidepressant  
 1293 medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with  
 1294 antidepressant medicines. **Talk to your, or your family member's, healthcare provider**  
 1295 **about:**

1296

- 1297 • all risks and benefits of treatment with antidepressant medicines
- 1298 • all treatment choices for depression or other serious mental illness

1299

1300 **What is the most important information I should know about antidepressant medicines,**  
 1301 **depression and other serious mental illnesses, and suicidal thought or actions?**

1302

- 1303 1. **Antidepressant medicines may increase suicidal thoughts and actions in some**  
 1304 **children, teenagers, and young adults within in the first few months of treatment.**  
 1305 2. **Depression and other serious mental illnesses are the most important causes of**  
 1306 **suicidal thoughts and actions. Some people may have a particularly high risk of**  
 1307 **having suicidal thoughts or actions.** These include people who have (or have a family  
 1308 history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts and  
 1309 actions.  
 1310 3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or**  
 1311 **family member?**
- 1312 • Pay close attention to any changes, especially sudden changes, in mood,  
 1313 behaviors, thoughts, or feelings. This is very important when an antidepressant  
 1314 medicine is started or when the dose is changed.
  - 1315 • Call the healthcare provider right away to report new or sudden changes in mood,  
 1316 behavior, thoughts, or feelings.
  - 1317 • Keep all follow-up visits with the healthcare provider as scheduled. Call the  
 1318 healthcare provider between visits as needed, especially if you have concerns about  
 1319 symptoms.

1320 **Call a healthcare provider right away if you or your family member has any of the**  
 1321 **following symptoms, especially if they are new, worse, or worry you:**  
 1322

- 1323 • thoughts about suicide or dying
- 1324 • attempts to commit suicide
- 1325 • new or worse depression
- 1326 • new or worse anxiety
- 1327 • feeling very agitated or restless
- 1328 • panic attacks
- 1329 • trouble sleeping (insomnia)
- 1330 • new or worse irritability
- 1331 • acting aggressive, being angry, or violent
- 1332 • acting on dangerous impulses
- 1333 • an extreme increase in activity and talking (mania)
- 1334 • other unusual changes in behavior or mood

1335  
 1336 **What else do I need to know about antidepressant medicines?**

- 1337 • **Never stop an antidepressant medicine without first talking to a healthcare**  
 1338 **provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- 1339 • **Antidepressants are medicines used to treat depression and other illnesses.** It is  
 1340 important to discuss all the risks of treating depression and also the risks of not  
 1341 treating it. Patients and their families or other caregivers should discuss all treatment  
 1342 choices with the healthcare provider, not just the use of antidepressants.
- 1343 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider  
 1344 about the side effects of the medicine prescribed for you or your family member.
- 1345 • **Antidepressant medicines can interact with other medicines.** Know all of the  
 1346 medicines that you or your family member takes. Keep a list of all medicines to show

1347 the healthcare provider. Do not start new medicines without first checking with your  
1348 healthcare provider.

1349 • **Not all antidepressant medicines prescribed for children are FDA approved for**  
1350 **use in children.** Talk to your child's healthcare provider for more information.

1351

1352 This Medication Guide has been approved by the U.S. Food and Drug Administration for all  
1353 antidepressants.

1354

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1357

1358

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