

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SERDOLECT safely and effectively. See full prescribing information for SERDOLECT.

SERDOLECT (sertindole) Tablets

Initial U.S. Approval: XXXX

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo.

SERDOLECT is not approved for the treatment of patients with dementia-related psychosis (5.1).

WARNING: SERTINDOLE PROLONGS THE QT INTERVAL IN A DOSE DEPENDENT MANNER

See full prescribing information for complete boxed warning.

Due to the capacity of SERDOLECT to prolong the QT interval, the prescriber should take the contraindications and warnings into consideration (5.2)

-----Indications and Usage-----

SERDOLECT is an atypical antipsychotic agent indicated for the treatment of schizophrenia and for reducing the risk of fatal and nonfatal suicide attempts in patients with schizophrenia

-----Dosage and Administration-----

SERDOLECT should be administered on a once a day schedule, with or without meals, generally beginning with 4 mg/day initially and increasing by 4 mg/day every 2-3 days until the recommended target dose of 16 mg is reached. Usual dose 12 to 20 mg/day.

-----Dosage Forms and Strengths-----

Tablets: 4 mg, 12 mg, 16 mg, and 20 mg

-----Contraindications-----

Patients with a history of QT prolongation (including congenital long QT syndrome)
Patients with a history of cardiac arrhythmias with recent myocardial infarction, or with uncompensated heart failure
Patients receiving drugs known to significantly prolong the QT interval
Patients receiving drugs that are potent inhibitors of CYP3A.
Patients with known hypersensitivity to sertindole or to any of the excipients.
Patients with severe hepatic impairment.

-----Warnings and Precautions-----

- *Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). SERDOLECT® is not approved for use in patients with dementia-related psychosis (5.1)
- *QT Prolongation:* increase in QT interval, avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.2)

- *Neuroleptic Malignant Syndrome (NMS):* Manage with immediate discontinuation of drug and close monitoring (5.3)
- *Tardive Dyskinesia:* Discontinue drug if clinically appropriate (5.4)
- *Hyperglycemia and Diabetes Mellitus:* Monitor glucose regularly in patients with and at risk for diabetes (5.5)
- *Orthostatic Hypotension:* Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.6)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.7)
- *Hyperprolactinemia:* Modest prolactin elevations occur and were mainly within normal range during chronic administration (5.8)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.9)
- *Body Temperature Regulation:* Use with caution in patients who may have elevation in core body temperature (5.10)
- *Suicide:* Closely supervise high-risk patients (5.11)

-----Adverse Reactions-----

Most commonly observed adverse reactions (incidence of $\geq 5\%$) and observed at a rate on sertindole were headache, insomnia, nasal congestion, and constipation.

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck USA at 1-800-xxxx or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-----Drug Interactions-----

Potent CYP2D6 and CYP3A inhibitors will increase Serdolect drug concentrations. Potent CYP2D6 inhibitors should only be used with caution with Serdolect and not in combination with any CYP3A inhibitors. CYP3A inducers will decrease Serdolect drug concentrations.

-----Use in Specific Populations-----

- *Renal Impairment* – No dosage adjustment is required in subjects with renal impairment.
- *Hepatic Impairment* – Patients with hepatic disease should have more gradual titration and lower maintenance doses.
- *Cardiac Impairment* – Because of the risk of orthostatic hypotension and QT prolongation associated with sertindole, caution should be observed in cardiac patients, especially those taking antiarrhythmic agents, given the potential for additive effects on QT prolongation.
- *Parkinson's Disease or Dementia with Lewy Bodies* are reported to have an increased sensitivity to antipsychotic medication.

See 17 For PATIENT COUNSELING INFORMATION

Revised: month/year

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WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

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*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analysis of 17 placebo controlled trials (modal duration of 10 weeks) in these subjects revealed a risk of death in the drug-treated subjects of between 1.6 to 1.7 times that seen in placebo-treated subjects. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated subjects was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. SERDOLECT (sertindole) tablets are not approved for the treatment of dementia-related psychosis.

WARNING: SERTINDOLE HAS BEEN SHOWN TO PROLONG THE QT INTERVAL IN A DOSE DEPENDENT MANNER

Sertindole causes an increase in the QT in a dose dependent manner, with a mean change from baseline in QT_{cF} of approximately 23 msec in sertindole 20 mg/day. At that dose, approximately 1.3% of patients experienced an increase in QT_c from normal at baseline to a level > 500 msec.

Some drugs that prolong the QT interval have been associated with the occurrence of Torsade de Pointes and with sudden unexplained death. Torsades de pointes has not been observed in association with the use of sertindole at recommended doses in premarketing studies. There have been very rare post-marketing reports of serious arrhythmia including Torsade de Pointes.

SERDOLECT should not be initiated in patients with a prolonged QT interval (QT_c greater than 450 [male] or 470 [female] msec) (see *Contraindications*).

SERDOLECT should be discontinued in patients who are found to have persistent QT_c measurements >500 msec.

After initiation of treatment with sertindole an ECG should be obtained after 3 to 4 weeks. An ECG is recommended after a further increase in dose, addition of drugs that prolong the QT interval or concomitant medication that may increase the sertindole concentration (potent CYP2D6 inhibitors, moderate CYP3A inhibitors).

SERDOLECT is contraindicated in patients with a history of QT prolongation and in patients with clinically significant cardiovascular disease, such as congestive heart failure, cardiac hypertrophy, arrhythmia, or bradycardia (<50 beats per minute) (see *Contraindications*).

4

5
6 **1. INDICATIONS AND USAGE**

7
8 SERDOLECT is indicated for the treatment of schizophrenia (*see Clinical Studies*).

9
10 SERDOLECT is also indicated for reducing the risk of fatal and nonfatal suicide attempts
11 in patients with schizophrenia (*see Clinical Studies*).

12
13
14 **2. DOSAGE AND ADMINISTRATION**

15
16 **2.1 Usual Dose**

17 SERDOLECT should be administered on a once a day schedule, with or without meals,
18 generally beginning with 4 mg/day initially and increasing by 4 mg/day every 2-3 days
19 until the recommended target dose of 16 mg is reached. Dependent on individual
20 patient response, the dose may be increased to 20 mg/day or decreased to 12 mg/day.

21 **2.2 Dosage Adjustment**

22 Dosage adjustments are not indicated on the basis of gender, race or renal impairment
23 status (*see Use in Specific Populations*).

24
25 *Dosage adjustment for patients with hepatic impairment taking SERDOLECT:*

26 Consideration should be given to a more gradual titration schedule and a lower target
27 dose in patients with mild to moderate hepatic impairment.

28
29 *Dosage adjustment for elderly patients taking SERDOLECT:* Consideration should be
30 given to a more gradual titration schedule and a lower target dose in patients who are
31 elderly.

32
33 *Dosage adjustment for patients taking SERDOLECT concomitantly with potent CYP2D6*
34 *inhibitors:* When concomitant administration of potent CYP2D6 inhibitors such as
35 quinidine, fluoxetine, or paroxetine with sertindole occurs, SERDOLECT dose should be
36 reduced to approximately one-half of its normal dose. When the CYP2D6 inhibitor is
37 withdrawn from the combination therapy, the SERDOLECT dose should be increased
38 (*see Drug Interactions*).

39
40 *Dosage adjustment for patients taking potential CYP3A inducers:* When a potential
41 CYP3A inducer such as carbamazepine is added to SERDOLECT therapy, the
42 SERDOLECT dose should be doubled. Additional dose increases should be based on
43 clinical evaluation. When the CYP3A inducer is withdrawn from the combination therapy,
44 the SERDOLECT dose should be reduced to the usual dose (*see Drug Interactions*).

45 **2.3 Maintenance Treatment**

46 Patients should be periodically reassessed to determine the need for maintenance
47 treatment. Patients with schizophrenia who had been symptomatically stable on other
48 antipsychotic medications for a period of 3 months or longer, were discontinued from
49 those medications, and were then administered SERDOLECT. Treatment with
50 SERDOLECT was efficacious during a period of up to 52 weeks (*see Clinical Studies*).

52 **Reinitiation of Treatment in Patients Previously Discontinued**
53 When restarting patients who have had an interval of less than one week off
54 SERDOLECT, titration of SERDOLECT is not required and the maintenance dose may
55 be reinitiated. When restarting therapy of patients who have been off SERDOLECT for
56 more than one week, the initial titration schedule should be followed.

57 **Switching From Other Antipsychotics**

58 There are no systematically collected data to specifically address switching patients with
59 schizophrenia from other antipsychotics to SERDOLECT or concerning concomitant
60 administration with other antipsychotics. While immediate discontinuation of the
61 previous antipsychotic treatment may be acceptable for some patients with
62 schizophrenia, more gradual discontinuation may be most appropriate for others. In all
63 cases, the period overlapping antipsychotic administration should be minimized.

64 **3. DOSAGE FORMS AND STRENGTHS**

65 SERDOLECT is available as:

- 66 4 mg: Oval, yellow, biconvex film-coated tablets marked with "S4" on one side
- 67 12 mg: Oval, beige, biconvex film-coated tablets marked with "S12" on one side
- 68 16 mg: Oval, red, biconvex film-coated tablets marked with "S16" on one side
- 69 20 mg: Oval, pink, biconvex film-coated tablets marked with "S20" on one side

70 **4. CONTRAINDICATIONS**

71 **QT-prolongation**

72 Because sertindole prolongs the QT interval in a dose dependent manner, it is
73 contraindicated in patients with a history of QT prolongation and in patients with clinically
74 significant cardiovascular disease such as congestive heart failure, cardiac hypertrophy,
75 arrhythmia, or bradycardia (<50 beats per minute) (*see Warnings and Precautions*).

76 Furthermore, SERDOLECT should not be initiated in patients with corrected QT interval
77 longer than 450 msec in males or 470 msec in females (*see Warnings and Precautions*).

78 SERDOLECT is contraindicated in patients receiving drugs known to significantly
79 prolong the QT interval. Relevant classes include:

- 80 - class Ia and III antiarrhythmics (e.g., quinidine, amiodarone, sotalol, dofetilide)
- 81 - some antipsychotics (e.g., thioridazine, ziprasidone)
- 82 - some macrolides (e.g., erythromycin)
- 83 - some quinolone antibiotics (e.g., gatifloxacin, moxifloxacin)
- 84 - some other drugs (e.g. lithium)

85 The above list is not exhaustive.

86 **Metabolism**

87 Given the dose dependent QT-prolongation observed with sertindole, drugs that inhibit
88 sertindole metabolism should be co administered with caution.

89 CYP2D6 is the principal isozyme involved in the metabolism of sertindole, with CYP3A
90 ordinarily having a secondary role (*see Pharmacokinetics, under Clinical Pharmacology*).

103 In CYP2D6 poor metabolizers (about 7% of Caucasians), the CYP3A system becomes
104 the principal route for sertindole's clearance from the body. Therefore, sertindole is
105 contraindicated in patients treated with potent inhibitors of CYP3A. Relevant classes
106 include:

- 107 - systemic treatment with 'azole' antifungal agents (e.g., ketoconazole, itraconazole)
- 108 - some macrolide antibiotics (e.g., erythromycin, clarithromycin)
- 109 - HIV protease inhibitors (e.g., indinavir)
- 110 - some calcium channel blockers (e.g., diltiazem, verapamil, nifedepine)
- 111 - Other potent inhibitors of CYP3A (e.g., cimetidine)

112 The above list is not exhaustive.

113

114 **Hypersensitivity**

115 SERDOLECT is contraindicated in patients with a known hypersensitivity to sertindole or
116 to any of the excipients.

117

118 **Electrolyte disturbances**

119 SERDOLECT is contraindicated in patients with known uncorrected hypokalaemia, and
120 those with known uncorrected hypomagnesaemia. This may occur in patients with
121 diarrhea or taking diuretics.

122

123 **Hepatic Impairment**

124 SERDOLECT is contraindicated in patients with severe hepatic impairment.

125

126

127 **5. WARNINGS AND PRECAUTIONS**

128 **5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

129 **Elderly patients with dementia-related psychosis treated with atypical**
130 **antipsychotic drugs are at an increased risk of death compared to placebo.**
131 **SERDOLECT (sertindole) is not approved for the treatment of dementia-related**
132 **psychosis (see *Boxed Warning*).**

133 **5.2 QT Prolongation**

134 **Sertindole causes an increase in the QT in a dose dependent manner, with a mean**
135 **change from baseline in QT_{CF} of approximately 23 msec in sertindole 20 mg/day.**
136 **At that dose, approximately 1.3% of patients experienced an increase in QTc from**
137 **normal at baseline to a level > 500 msec.**

138

139 **Some drugs that prolong the QT interval have been associated with the**
140 **occurrence of Torsade de Pointes and with sudden unexplained death. Torsades**
141 **de Pointes has not been observed in association with the use of sertindole at**
142 **recommended doses in premarketing studies. There have been very rare post-**
143 **marketing reports of serious arrhythmia including Torsade de Pointes,**

144

145 **SERDOLECT should be discontinued in patients who are found to have**
146 **persistent QTc measurements >500 msec.**

147

148 **After initiation of treatment with sertindole an ECG should be obtained after 3**
149 **to 4 weeks. An ECG is recommended after a further increase in dose, addition**
150 **of drugs that prolong the QT interval, or concomitant medication that may**

151 **increase the sertindole concentration (potent CYP2D6 inhibitors, moderate**
152 **CYP3A inhibitors).**
153

154 As with other antipsychotic drugs and placebo, sudden unexplained deaths have been
155 reported in patients taking SERDOLECT at recommended doses. The experience from
156 clinical trials did not reveal an excess mortality for SERDOLECT compared to other
157 antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the
158 drugs used as active controls and placebo. In epidemiological studies, including
159 comparative cohort studies, conducted in more than 8,500 patients, SERDOLECT was
160 not associated with an increase in overall mortality or documented cardiac mortality.

161
162 One documented case of self-limiting Torsade de Pointes has been observed in
163 association with the use of SERDOLECT at recommended doses in a large simple trial.
164 Moreover, in premarketing studies two cases of intentional overdose (in excess 20 times
165 recommended doses) have included reports of Torsade de Pointes. These cases were
166 also associated with substantial overdose of concomitant medications, some of which
167 have independently been documented to be associated with Torsade de Pointes. Both
168 patients recovered.

169
170 In a randomized, risperidone-controlled, open-label, prospective use SERDOLECT study
171 (n=9858) the treatment groups had comparable mortality. The number of documented
172 arrhythmias with SERDOLECT was small (n=3).

173 Certain circumstances may increase the risk of Torsade de Pointes and/or sudden death
174 in association with the use of drugs that prolong the QT interval, including (1)
175 bradycardia, (2) hypokalaemia or hypomagnesaemia (3) concomitant use of other drugs
176 that prolong the QT interval and (4) presence of congenital prolongation of the QT
177 interval.

178
179 The value of routine screening ECG measures in detecting patients at risk is
180 questionable. Rather, SERDOLECT should be avoided in patients with a history of QT
181 prolongation or significant cardiovascular illness (*see Contraindications*).

182 For patients taking SERDOLECT who experience symptoms that could indicate the
183 occurrence of Torsade de Pointes e.g. dizziness, palpitations, or syncope, the prescriber
184 should initiate further evaluation.

185 It is recommended that patients being considered for SERDOLECT treatment who are at
186 risk for significant electrolyte disturbances, hypokalemia in particular, have baseline
187 serum potassium and magnesium measurements. Hypokalemia (and/or
188 hypomagnesemia) may increase the risk of QT prolongation and arrhythmia.
189 Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with
190 low serum potassium and/or magnesium should be repleted with those electrolytes
191 before proceeding with treatment. It is essential to periodically monitor serum
192 electrolytes in patients for whom diuretic therapy is introduced during SERDOLECT
193 treatment. Persistently prolonged QTc intervals may also increase the risk of further
194 prolongation and arrhythmia, but it is not clear that routine screening ECG measures are
195 effective in detecting such patients. Rather, SERDOLECT should be avoided in patients
196 with histories of significant cardiovascular illness (*see Contraindications*).

197 Potent CYP2D6 inhibitors like fluoxetine and paroxetine should be used with caution
198 together with SERDOLECT and not in combination with any CYP3A inhibitors and
199 SERDOLECT (*see Drug Interactions*).

200 **5.3 Neuroleptic Malignant Syndrome (NMS)**

201 A potential fatal symptom complex sometimes referred to as Neuroleptic Malignant
202 Syndrome (NMS) has been reported in association with administration of antipsychotic
203 drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental
204 status and evidence of autonomic instability (irregular pulse or blood pressure,
205 tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include
206 elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal
207 failure.

208

209 The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a
210 diagnosis, it is important to exclude cases where the clinical presentation includes both
211 serious medical illness (e.g. pneumonia, systemic infection, etc.) and untreated or
212 inadequately treated extrapyramidal signs and symptoms (EPS). Other important
213 considerations in the differential diagnosis include central anticholinergic toxicity, heat
214 stroke, drug fever, and primary central nervous system (CNS) pathology.

215

216 The management of NMS should include: 1) immediate discontinuation of antipsychotic
217 drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic
218 treatment and medical monitoring; and 3) treatment of any concomitant serious medical
219 problems for which specific treatments are available. There is no general agreement
220 about specific pharmacological treatment regimens for NMS.

221

222 If a patient requires antipsychotic drug treatment after recovery from NMS, the potential
223 reintroduction of drug therapy should be carefully considered. The patients should be
224 carefully monitored, since recurrences of NMS have been reported.

225 **5.4 Tardive Dyskinesia**

226 A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in
227 patients treated with antipsychotic drugs. Although the prevalence of the syndrome
228 appears to be highest among the elderly, especially elderly women, it is impossible to
229 rely upon prevalence estimates to predict, at the inception of antipsychotic treatment,
230 which patients are likely to develop the syndrome. Whether antipsychotic drug products
231 differ in their potential to cause tardive dyskinesia is unknown.

232

233 The risk of developing tardive dyskinesia and the likelihood that it will become
234 irreversible are believed to increase as the duration of treatment and the total cumulative
235 dose of antipsychotic drugs administered to the patient increase. However, the
236 syndrome can develop, although much less commonly, after relatively brief treatment
237 periods at low doses.

238

239 There is no known treatment for established cases of tardive dyskinesia, although the
240 syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.
241 Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs
242 and symptoms of the syndrome and thereby may possibly mask the underlying process.
243 The effect that symptomatic suppression has upon the long-term course of the syndrome
244 is unknown.

245
246 Given these considerations, SERDOLECT should be prescribed in a manner that is most
247 likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment
248 should generally be reserved for patients who suffer from a chronic illness that (1) is
249 known to respond antipsychotic drugs, and (2) for whom alternative, equally effective,
250 but potentially less harmful treatments are not available or appropriate. In patients who
251 do require chronic treatment, the smallest dose and the shortest duration of treatment
252 producing a satisfactory clinical response should be sought. The need for continued
253 treatment should be reassessed periodically.

254
255 If signs and symptoms of tardive dyskinesia appear in a patient on SERDOLECT, drug
256 discontinuation should be considered. However, some patients may require treatment
257 with SERDOLECT despite the presence of the syndrome.

258 **5.5 Hyperglycemia and Diabetes Mellitus**

259 Hyperglycemia, in some cases extreme and associated with ketoacidosis or
260 hyperosmolar coma or death, has been reported in patients treated with all atypical
261 antipsychotics. These cases were, for the most part, seen in post-marketing clinical use
262 and epidemiologic studies, not in clinical trials, and there have been rare reports of
263 hyperglycemia or diabetes in trial subjects treated with SERDOLECT. Assessment of the
264 relationship between atypical antipsychotic use and glucose abnormalities is
265 complicated by the possibility of an increased background risk of diabetes mellitus in
266 patients with schizophrenia and the increasing incidence of diabetes mellitus in the
267 general population. Given these confounders, the relationship between atypical
268 antipsychotic use and hyperglycemia-related adverse events is not completely
269 understood. However, epidemiological studies suggest an increased risk of treatment-
270 emergent hyperglycemia-related adverse events in patients treated with atypical
271 antipsychotics. Because SERDOLECT was not marketed at the time these studies were
272 performed, it is not known if SERDOLECT is associated with this increased risk but as
273 mentioned above, the experience from clinical trials do not support this assumption.

274
275 Patients with an established diagnosis of diabetes mellitus who are started on atypical
276 antipsychotics should be monitored regularly for worsening of glucose control. Patients
277 with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are
278 starting treatment with atypical antipsychotics should undergo fasting blood glucose
279 testing at the beginning of treatment and periodically during treatment. Any patient
280 treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia
281 including polydipsia, polyuria, polyphagia, and weakness. Patients who develop
282 symptoms of hyperglycemia during treatment with atypical antipsychotics should
283 undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when
284 the atypical antipsychotic was discontinued; however, some patients required
285 continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
286

287 **5.6 Orthostatic Hypotension**

288 SERDOLECT may induce orthostatic hypotension associated with dizziness,
289 tachycardia, and in some patients, syncope, especially during the initial dose-titration
290 period, probably reflecting its α 1-adrenergic antagonistic properties. Syncope (MedDRA
291 version 10.1 PT) was reported in 1% (31/2711) SERDOLECT-treated patients in phase
292 2-3 studies. Patients experiencing dizziness, palpitations, or syncope after initial titration

293 with SERDOLECT may benefit from additional cardiovascular evaluation to rule out the
294 potential risk of arrhythmia.

295
296 The risk of orthostatic hypotension and syncope may be limited by following the
297 recommended dosing guidelines. In some patients, slower titration may be medically
298 appropriate (*see Dosage and Administration*). A more gradual titration to the target dose
299 should be considered if hypotension occurs. SERDOLECT should be used with
300 particular caution in patients with conditions predisposing to hypotension (dehydration,
301 hypovolemia, and treatment with antihypertensive medications).

302 **5.7 Seizures**

303 During clinical trials, seizures occurred in 1% (34/2711) of SERDOLECT-treated
304 patients. Like other antipsychotic drugs, SERDOLECT should be used cautiously in
305 patients with a history of seizures or other conditions that potentially lower the seizure
306 threshold. Conditions that lower the seizure threshold may be more prevalent in patients
307 65 years or older.

308 **5.8 Hyperprolactinemia**

309 Like other drugs that antagonize dopamine D2 receptors, SERDOLECT elevates
310 prolactin levels. Mean plasma prolactin concentrations following both acute, single-dose
311 sertindole administration in healthy subjects, and chronic treatment of patients with
312 schizophrenia for almost 2 years were mainly within the normal range and sporadically
313 above the upper limit of normal, but the changes were not considered clinically relevant.
314 Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence
315 have been reported with prolactin-elevating compounds, the clinical significance of
316 elevated serum prolactin levels is unknown for most patients. An increase in pituitary
317 gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was
318 observed in the sertindole carcinogenicity studies conducted in mice and rats (*see*
319 *Nonclinical Toxicology*). Although tissue culture experiments indicate that approximately
320 one-third of human breast cancers are prolactin-dependent in vitro, neither clinical
321 studies nor epidemiologic studies conducted to date have shown an association
322 between chronic administration of this class of drugs and carcinogenesis in humans; the
323 available evidence is considered too limited to be conclusive at this time.

324 **5.9 Potential for Cognitive and Motor Impairment**

325 Although SERDOLECT was not distinguishable from placebo with regards to the
326 occurrence of somnolence in short-term studies, many psychotropic drugs do have the
327 potential to impair judgment, thinking or motor skills. Consequently, patients treated with
328 SERDOLECT should be cautioned about performing activities requiring mental
329 alertness, such as operating hazardous machinery, including automobiles, until they are
330 reasonably certain that SERDOLECT therapy does not affect them in this manner

331 **5.10 Body Temperature Regulation**

332 Although not reported with SERDOLECT, disruption of body temperature regulation has
333 been attributed to other antipsychotic agents. Caution is advised when prescribing for
334 patients who will be experiencing conditions which may contribute to an elevation in core
335 body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving
336 concomitant medication with anticholinergic activity, or being subject to dehydration.

337 **5.11 Suicide**

338 SERDOLECT has shown a significantly reduced risk of fatal and nonfatal suicide
339 attempts in patients with schizophrenia. However, the possibility of a suicide attempt is
340 inherent in schizophrenia and close supervision of high-risk patients should accompany
341 drug therapy. Prescriptions for SERDOLECT should be written for the smallest quantity
342 of tablets consistent with good patient management, in order to reduce the risk of
343 overdose.

344 **5.12 Dysphagia**

345 Esophageal dysmotility and aspiration have been associated with antipsychotic drug
346 use. SERDOLECT and other antipsychotic drugs should be used cautiously in patients
347 at risk for aspiration pneumonia.

348 **5.13 Priapism**

349 Drugs with alpha-adrenergic blocking effects have been reported to induce priapism.
350 Although no cases of priapism have been reported in clinical trials with SERDOLECT,
351 SERDOLECT shares this pharmacologic activity and, therefore, may be associated with
352 this risk. Severe priapism may require surgical intervention.

353 **5.14 Use in Patients with Concomitant illness**

354 Clinical experience with SERDOLECT in patients with concomitant systemic illnesses is
355 limited.

356
357 Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have
358 an increased sensitivity to antipsychotic medication. Manifestations of this increased
359 sensitivity include confusion, obtundation, and postural instability with frequent falls,
360 extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant
361 syndrome.

362
363 SERDOLECT has not been evaluated or used to any appreciable extent in patients with
364 a recent history of myocardial infarction or unstable heart disease. Patients with these
365 diagnoses were excluded from clinical studies. Because of the risk of orthostatic
366 hypotension and QT-prolongation associated with SERDOLECT, caution should be
367 observed in cardiac patients, especially those treated with antiarrhythmic agents, given
368 the potential for additive effects on QT-prolongation (*see Contraindications*).

369 **5.15 Laboratory Tests**

370 No specific routine laboratory tests are recommended.
371 Baseline serum potassium and magnesium should be measured and low serum
372 potassium and magnesium should be corrected before starting with treatment with
373 SERDOLECT. Patients who are treated with diuretics during SERDOLECT therapy need
374 periodic monitoring of serum potassium and magnesium. Patients with diabetes should
375 closely monitor their blood glucose levels (*see Warnings and Precautions*).

376
377

378 **6. ADVERSE REACTIONS**

379

380 Because clinical studies are conducted under widely varying conditions, adverse
381 reaction rates observed in the clinical studies of a drug cannot be directly compared to

382 rates in the clinical studies of another drug and may not reflect the rates observed in
383 practice.

384

385 The clinical development program for SERDOLECT included 2711 patients with
386 schizophrenia. SERDOLECT was administered at a dose ranging from <2 to 24 mg
387 once daily and duration of exposure ranged from 1 week to >5 years. This represented a
388 total of 1831 patient-years of exposure to SERDOLECT. Including post-marketing
389 exposure, the total exposure of SERDOLECT as of 11 January 2008 was in excess of
390 27.000 patient-years.

391 **6.1 Common Adverse Reactions Observed in Placebo Controlled Trials**

392 In Short-Term, Placebo-controlled trials, the most commonly observed adverse reaction
393 associated with the use of SERDOLECT (incidence of 5% or greater) were headache
394 (28%), insomnia (21%), nasal congestion (21%) and constipation (13%). Rates of
395 discontinuation were less than 1 % for the most commonly observed adverse reactions.

396

397 Adverse reactions in Short-Term, Placebo-Controlled Trials that occurred in at least 5 %
398 of patients treated with SERDOLECT (5 % or higher) are shown below:

Incidence of Adverse Events by System Organ Class: Placebo-Controlled Studies

MedDRA Preferred Term	Placebo (N = 290) n (%)	Total Sertindole (N = 704) n (%)
Any Adverse Event	249 (85.9)	618 (87.8)
Gastrointestinal disorders	122 (42.1)	335 (47.6)
Constipation	27 (9.3)	93 (13.2)
Dry mouth	13 (4.5)	65 (9.2)
Dyspepsia	31 (10.7)	64 (9.1)
Nausea	27 (9.3)	62 (8.8)
Vomiting	32 (11.0)	56 (8.0)
Toothache	21 (7.2)	43 (6.1)
General disorders and administration site conditions	67 (23.1)	179 (25.4)
Fatigue	16 (5.5)	49 (7.0)
Pain	16 (5.5)	38 (5.4)
Infections and infestations	40 (13.8)	124 (17.6)
Nasopharyngitis	11 (3.8)	42 (6.0)
Musculoskeletal and connective tissue disorders	64 (22.1)	200 (28.4)
Pain in extremity	15 (5.2)	50 (7.1)
Back pain	15 (5.2)	39 (5.5)
Musculoskeletal stiffness	11 (3.8)	39 (5.5)
Nervous system disorders	153 (52.8)	395 (56.1)
Headache	84 (29.0)	197 (28.0)
Dizziness	20 (6.9)	88 (12.5)
Sedation	13 (4.5)	47 (6.7)
Extrapyramidal disorder	15 (5.2)	43 (6.1)
Somnolence	13 (4.5)	42 (6.0)
Psychiatric disorders	88 (30.3)	224 (31.8)
Insomnia	61 (21.0)	147 (20.9)
Reproductive system and breast disorders	21 (7.2)	108 (15.3)
Ejaculation failure ^a	3 (1.2)	54 (9.3)
Dysmenorrhoea ^b	3 (6.4)	8 (6.6)

Incidence of Adverse Events by System Organ Class: Placebo-Controlled Studies

MedDRA Preferred Term	Placebo (N = 290) n (%)	Total Sertindole (N = 704) n (%)
Respiratory, thoracic and mediastinal disorders	49 (16.9)	249 (35.4)
Nasal congestion	23 (7.9)	149 (21.2)
Cough	15 (5.2)	41 (5.8)
Pharyngolaryngeal pain	14 (4.8)	40 (5.7)

^a Percentage based on male patients.
^b Percentage based on female patients.

400

401 6.2 Less Commonly Observed Adverse Reactions

402 Incidence of Adverse Events by System Organ Class Reported for $\geq 2\%$ and $< 5\%$ of
403 Patients in the Total Sertindole Groups where the Incidence is higher for Total Sertindole
404 Compared to Placebo:

405

406 Placebo-Controlled Studies

407

Incidence of Adverse Events by System Organ Class: Placebo-Controlled Studies

System Organ Class/MedDRA Preferred Term	Placebo (N = 290) n (%)	Total (N = 704) n (%)
Any Adverse Event	249 (85.9)	618 (87.8)
Eye disorders	25 (8.6)	65 (9.2)
Vision blurred	8 (2.8)	24 (3.4)
Gastrointestinal disorders	122 (42.1)	335 (47.6)
Stomach discomfort	6 (2.1)	29 (4.1)
Abdominal discomfort	13 (4.5)	22 (3.1)
Flatulence	9 (3.1)	22 (3.1)
Abdominal pain upper	10 (3.4)	20 (2.8)
Diarrhoea	9 (3.1)	14 (2.0)
General disorders and administration site conditions	67 (23.1)	179 (25.4)
Asthenia	13 (4.5)	25 (3.6)
Chest pain	6 (2.1)	25 (3.6)
Pyrexia	2 (0.7)	16 (2.3)

Incidence of Adverse Events by System Organ Class: Placebo-Controlled Studies

System Organ Class/MedDRA Preferred Term	Placebo (N = 290) n (%)	Total (N = 704) n (%)
Oedema peripheral	2 (0.7)	14 (2.0)
Immune system disorders	1 (0.3)	3 (0.4)
Hypersensitivity	0	3 (0.4)
Seasonal allergy	1 (0.3)	0
Infections and infestations	40 (13.8)	124 (17.6)
Rhinitis	3 (1.0)	18 (2.6)
Investigations	16 (5.5)	86 (12.2)
Weight increased	3 (1.0)	25 (3.6)
Musculoskeletal and connective tissue disorders	64 (22.1)	200 (28.4)
Myalgia	10 (3.4)	24 (3.4)
Arthralgia	3 (1.0)	20 (2.8)
Neck pain	9 (3.1)	17 (2.4)
Nervous system disorders	153 (52.8)	395 (56.1)
Akathisia	14 (4.8)	24 (3.4)
Tremor	14 (4.8)	25 (3.6)
Dizziness postural	3 (1.0)	19 (2.7)
Movement disorder	6 (2.1)	19 (2.7)
Lethargy	8 (2.8)	24 (3.4)
Psychiatric disorders	88 (30.3)	224 (31.8)
Restlessness	8 (2.8)	28 (4.0)
Renal and urinary disorders	21 (7.2)	47 (6.7)
Urinary incontinence	10 (3.4)	20 (2.8)
Reproductive system and breast disorders	21 (7.2)	108 (15.3)
Erectile dysfunction ^a	1 (0.4)	17 (7.1)
Ejaculation disorder ^a	2 (0.8)	25 (4.2)
Respiratory, thoracic and mediastinal disorders	49 (16.9)	249 (35.4)
Dyspnoea	1 (0.3)	19 (2.7)
Rhinorrhoea	3 (1.0)	19 (2.7)
Epistaxis	4 (1.4)	15 (2.1)

Incidence of Adverse Events by System Organ Class: Placebo-Controlled Studies

System Organ Class/MedDRA Preferred Term	Placebo (N = 290) n (%)	Total (N = 704) n (%)
Wheezing	4 (1.4)	15 (2.1)
Skin and subcutaneous tissue disorders	45 (15.5)	105 (14.9)
Rash	14 (4.8)	23 (3.3)
Pruritus	6 (2.1)	22 (3.1)

^a Percentage based on male patients.

408

409 * Adverse reaction are defined as adverse events that occurred in at least 1 % of
410 patients treated with SERDOLECT and for which the incidence in was higher than the
411 incidence in placebo. Standard MedDRA (version 10.1) dictionary terminology has been
412 used to classify reported adverse events.

413 6.3 Discontinuations Due To Adverse Reactions

414 In the short-term, placebo-controlled trials, there was no significant difference in the
415 overall rates of discontinuation for adverse events, i.e. 7% for SERDOLECT and 5% for
416 placebo.

417 The most common discontinuation rates for adverse events were Electrocardiogram
418 abnormal (0.6%), Liver function test abnormal (0.6%), Ejaculation failure (0.6%),
419 Sedation (0.4%), Tachycardia (0.3%), Electrocardiogram QT corrected interval
420 prolonged (0.3%), Electrocardiogram QT prolonged (0.3%), Hepatic enzyme abnormal
421 (0.3%), Dizziness (0.3%), Somnolence (0.3%), Ejaculation disorder (0.3%), Orthostatic
422 hypotension (0.3%).

423 6.4 Dose Related Adverse Reactions

424 For adverse events >5% a dose response pattern was observed for nasal congestion.
425 For adverse events ≥2% and <5% a dose response pattern was observed for dry mouth
426 and pharyngolaryngeal pain.

427 6.5 Clinically Significant Adverse Reactions

428 ECG changes: SERDOLECT is associated with a dose dependent increase of the QT
429 interval (see *Warnings and Precautions*).

430 Cardiovascular: SERDOLECT is associated with initial orthostatic hypotension and
431 tachycardia (see *Warnings and Precautions*).

432

433 Nervous system: An 8-week, placebo-controlled trial involving three doses of
434 SERDOLECT (12, 20 and 24 mg/day), three doses of haloperidol (4, 8 and 16 mg/day),
435 and placebo revealed that SERDOLECT was indistinguishable from placebo with regard
436 to emergent Extrapyramidal symptoms (EPS) and anti-EPS medication use at all three
437 doses.

438 Ophthalmological findings: Because of lens opacities observed in rodent studies with
439 SERDOLECT (see *Nonclinical Toxicology*), ophthalmological examinations were done
440 pre- and post-treatment in 139 patients treated with SERDOLECT in a long-term

441 extension trial. The examinations included assessments of visual acuity, visual fields,
442 and papillary size, slit lamp evaluation, measurement of intraocular pressure, vital
443 staining of the cornea and conjunctiva and funduscopy. No pattern of clinically important
444 changes was detected upon review of the ophthalmological examination data by an
445 independent ophthalmologist.

446 **6.6 Laboratory changes**

447 Mean changes from baseline and proportions of patients meeting criteria for possibly
448 important change from baseline were compared for SERDOLECT and placebo patients
449 for a pool of 5 short-term, placebo-controlled trials. Several SERDOLECT related
450 findings were observed, including asymptomatic increases in cholesterol, triglycerides,
451 glucose, and prolactin (see *Warnings and Precautions*).

452 In addition, as seen with other drugs with α_1 -adrenergic blocking activity, minor changes
453 in some hematology values were seen in patients treated with SERDOLECT, probably
454 due to hemodilution (see *Warnings and Precautions*).

455 Fluctuations in liver transaminase levels were observed, which were generally transient
456 and not dose-dependent. The incidence of patients with adverse events related to liver
457 function in placebo-controlled trials was 1.6% (11/704) of patients treated with sertindole
458 and 0% (0/290) of placebo patients. A safety review of all potential liver related events
459 (n=30) reported for SERTINDOLE was performed and concluded that no signal was
460 identified.

461 Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare
462 cases during treatment with SERDOLECT. Appropriate clinical monitoring is advisable in
463 diabetic patients and in patients with risk factors for the development of diabetes
464 mellitus.

465 In the metabolic sub-study (see below) there was a mean increase in fasting glucose of
466 0.12 mmol/L among SERDOLECT patients compared to a decrease of 0.04 mmol/L in
467 risperidone patients. These are minor changes and of no clinical relevance.

468 Across all phase 2 and 3 studies, the proportion of patients with glucose changes of
469 potential clinical importance was not substantially different among treatments. Among all
470 patients receiving SERDOLECT, 4.8% (n=2084) had glucose values of potential clinical
471 importance compared to 3.3% of placebo patients (n=275).

472 **6.7 Metabolic syndrome**

473 In a randomized, active-controlled, clinical study patients were randomized to either
474 SERDOLECT or risperidone (active control). The drugs were taken under normal use;
475 there were no protocol specified guidelines for diet, exercise, modification of any factors
476 identified with metabolic syndrome.

477
478 Metabolic Syndrome was diagnosed according to the criteria of the International
479 Diabetes Federation 1. For a person to be defined as having the metabolic syndrome the
480 person had to meet the following criteria:

- 481 • *Central obesity* defined as a waist circumference ≥ 94 cm for European men and ≥ 80
482 cm for European women, and

483

484 Any 2 (or more) of the following 4 factors:

- 485 • Raised triglyceride (TG) level defined as TG ≥ 150 mg/dL (1.7 mmol/L), or specific
486 treatment for this lipid abnormality
- 487 • Reduced HDL cholesterol defined as HDL < 40 mg/dL (1.03 mmol/L) in men and HDL
488 < 50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality

- 489 • Raised blood pressure (BP) defined as systolic BP \geq 130 mmHg or diastolic BP \geq
 490 85 mmHg, or treatment of previously diagnosed hypertension
 491 • Raised fasting plasma glucose (FPG) defined as FPG \geq 100 mg/dL (5.6 mmol/L), or
 492 previously diagnosed type 2 diabetes
 493

494 The results are shown below:
 495
 496

Parameter	N	SERDOLECT	N	Risperidone
Weight (kg)				
Baseline	107	71.7	116	73.4
Change from baseline				
6 Month	78	1.61	97	1.43
Endpoint	107	1.75	116	1.68
BMI (Kg/m ²)				
Baseline	107	24.71	116	25.59
Change from baseline				
6 Months	78	0.56	97	0.51
Endpoint	107	0.61	116	0.61
Waist Circumference (cm)				
Baseline	107	84.75	116	85.83
Change from baseline				
6 Months	78	1.02	97	1.57
Endpoint	107	1.37	116	1.57
Systolic Blood Pressure (mm Hg)				
Baseline	107	117.34	116	120.10
Change from baseline				
6 Months	78	0.53	97	-1.32
Endpoint	107	0.36	116	-0.84
Diastolic Blood Pressure (mm Hg)				
Baseline	107	74.64	116	76.65
Change from baseline				
6 Months	78	-0.26	97	-1.29
Endpoint	107	0.25	116	-0.12
Fasting Glucose (mmol/L)				
Baseline	85	5.25	102	5.43
Change from baseline				
6 Months	52	0.05	79	-0.11
Endpoint	85	0.12	102	-0.04

497

498 **6.8 Serum Cholesterol and Triglycerides**
 499

Parameter (mmol/L)	N	SERDOLECT	N	Risperdone
Cholesterol				
Baseline	89	4.83	103	5.04
Change from baseline				
6 Month	55	0.10	80	-0.22
Endpoint	89	0.05	103	-0.09
Triglycerides				
Baseline	89	1.25	103	1.52

Change from baseline				
6 Months	55	0.12	80	-0.04
Endpoint	89	0.03	103	-0.04
HDL				
Change from baseline	89	1.29	103	1.26
6 Months	55	0.08	80	-0.02
Endpoint	89	0.06	103	0.02
LDL				
Change from baseline	89	2.97	100	3.06
6 Months	55	-0.03	76	-0.17
Endpoint	89	-0.03	100	-0.10

500

501 From this study it was concluded that treatment with sertindole did not appear to be
502 associated with an increased risk of developing metabolic syndrome, as defined by the
503 IDF, compared to treatment with risperidone.

504 In general, the metabolic effects of sertindole and risperidone were similar: both
505 treatments were associated with modest weight gain, and a corresponding increase in
506 BMI and in waist circumference.

507 Treatment with sertindole was not associated with clinically relevant changes in
508 triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, blood pressure, or
509 blood glucose.

510

511 In a pool of all placebo-controlled short-term trials, no increase in mean fasting
512 cholesterol from baseline to endpoint was observed for SERDOLECT treated patients
513 (n=703) compared to a decrease of 0.2 mmol/L (n=290) for placebo patients. In the
514 same group of patients and there was an increase in mean fasting triglycerides from
515 baseline to endpoint for SERDOLECT patients of 0.2 mmol/L (n=703) compared to no
516 changes for placebo patients (n=290). These changes are in line with those obtained in
517 the above-mentioned study and of no clinical relevance.

518

519 6.9 Weight Gain

520 In the study described above (*see Metabolic Syndrome*), only moderate increases in
521 weight and BMI were observed. The mean increase in weight from baseline to end-point
522 was 1.76 kg (n=107) for SERDOLECT patients compared to 1.68 kg (n=116) for
523 risperidone patients. In both treatment groups 18 patients had an increase in weight \geq
524 7% from baseline to endpoint - corresponding to 16.8% of SERDOLECT patients and
525 15.5% of risperidone patients. The conclusions in the study report state that these
526 changes were of no clinical relevance in relation to development of metabolic syndrome.

527

528 In a pool of all placebo-controlled short-term SERDOLECT trials, 19.6% (138/704) of
529 SERDOLECT patients compared to 7.6% (22/290) of placebo patients met criteria for
530 weight increases of \geq 7% from baseline. Across all phase 2 and 3 studies (n=2474) there
531 was a mean increase in weight from baseline for SERDOLECT patients of 4.0 kg.
532 Approximately 29% (769/2711) of patients in these trials had weight gain of \geq 7% (*see*
533 *Warnings and Precautions*).

534

535 6.10 Postmarketing Experience

536 The following adverse reactions have been observed during market use of
537 SERDOLECT: Torsade de pointes, Ventricular tachycardia, Syncope, Convulsions

538 NOS, Grand Mal convulsion, movement disorders (in particular tardive dyskinesia),
539 Neuroleptic malignant syndrome (NMS) and Hyperglycemia
540
541 Because these reactions are reported voluntarily from a population of uncertain size, it is
542 not always possible to reliably estimate their frequency or establish a causal relationship
543 to drug exposure.
544

545 **7. DRUG INTERACTIONS**

546
547
548 Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or
549 pharmacokinetic (alteration of plasma levels). The risks of using SERDOLECT in
550 combination with other drugs have been evaluated as described below. All interactions
551 studies have been conducted with sertindole. Based upon the pharmacodynamic and
552 pharmacokinetic profile of sertindole, possible interactions could be anticipated:
553

554 Given the primary CNS effects of SERDOLECT, caution should be used when it is taken
555 in combination with other centrally acting drugs and alcohol. Because of its potential for
556 inducing hypotension, SERDOLECT may enhance the effects of certain antihypertensive
557 agents. SERDOLECT may antagonize the effects of levodopa and dopamine agonists.

558 **7.1 Potential for Other Drugs to Affect SERDOLECT**

559 Sertindole is metabolized by the CYP2D6 and CYP3A isozymes. Potent inhibitors of
560 CYP2D6 (eg, fluoxetine, paroxetine) can inhibit the metabolism of sertindole and cause
561 increased plasma levels. Potent inhibitors of CYP3A are contraindicated (see
562 *Contraindications*). CYP-inducers (eg, carbamazepine) may increase the metabolism of
563 sertindole and lower plasma levels.
564

565 **CYP2D6 Inhibitors**

566 Population pharmacokinetic analyses detected that the plasma concentration of
567 sertindole is increased by a factor of 2-3 in patients concurrently taking fluoxetine or
568 paroxetine (potent CYP2D6 inhibitors). SERDOLECT and potent CYP2D6 inhibitors
569 should only be co-administered with caution. A lower maintenance dose of SERDOLECT
570 may be needed and ECG recording should be undertaken before and after any dose
571 adjustment of these drugs.
572

573 While quinidine, a potent inhibitor of CYP2D6 has not been studied in clinical trials, in
574 vitro data revealed an inhibitory effect of quinidine on the formation of dehydrosertindole
575 (by 17%) and norsertindole (by 20-28%). In addition quinidine has antiarrhythmic
576 properties and is contraindicated to be used with SERDOLECT (see *Contraindications*).

577 **CYP3A Inhibitors**

578 Population pharmacokinetic analyses found minor increases (<25%) in sertindole
579 plasma concentrations for macrolide antibiotics (e.g., erythromycin, a CYP3A inhibitor)
580 and calcium channel antagonists (diltiazem, verapamil and nifedipine). However, the
581 consequences could be greater in CYP2D6 poor metabolizers (since elimination of
582 sertindole by both CYP2D6 and CYP3A would be affected). Therefore, the concomitant
583 administration of CYP3A inhibitors and SERDOLECT is contraindicated, as this may
584 lead to significant increases in sertindole levels (see *Contraindications*).
585

586 **CYP – Inducers**

587 Population pharmacokinetic analyses found that the metabolism of sertindole may be
588 significantly enhanced by agents known to induce CYP isozymes, such as rifampicin,
589 carbamazepine, phenytoin and phenobarbital, which can decrease the plasma
590 concentrations of sertindole by a factor of 2 to 3. Reduced antipsychotic efficacy in
591 patients receiving these drugs or other inducing agents may require the dose of
592 SERDOLECT to be adjusted to the upper dosage range.

593 **7.2 Potential for SERDOLECT to Affect Other Drugs**

594 **Dextromethorphan**

595 Consistent with *in vitro* results, a study in healthy subjects showed that extensive
596 CYP2D6 metabolizers did not change metabolizer status after multiple doses of
597 sertindole (8 mg/day). Only a minor increase in the urinary
598 dextromethorphan/dextrorphan ratio was observed indicating that sertindole is a weak
599 inhibitor of CYP2D6.

600

601 **Drugs having No Clinically Important Interactions with SERDOLECT**

602

603 **Alprazolam**

604 Multiple doses of sertindole (12 mg/day) had only minor effects on the pharmacokinetics
605 of a single dose (1 mg) alprazolam (CYP3A substrate). No dose adjustment is
606 recommended.

607 **Digoxin**

608 Multiple doses of sertindole (12 mg/day) had no effect on C_{max} or AUC of digoxin after
609 multiple doses (0.25 mg/day). No dose adjustment is recommended.

610

611 **Valproic acid**

612 Valproic acid increased the clearance of sertindole with 20%. No dose adjustment is
613 recommended.

614

615 Population pharmacokinetic analyses found no evidence of effects for the following
616 medications or medication classes on sertindole pharmacokinetics, haloperidol,
617 bupropion, buspirone, thiothixene, diphenhydramine, estrogen, oral contraceptives,
618 various benzodiazepines, pseudoephedrine, thyroid hormones, and lipid lowering agents
619 (pravastatin and lovastatin)

620

621

622 **8. USE IN SPECIFIC POPULATIONS**

623 **8.1 Pregnancy**

624 Teratogenic Effects – Pregnancy Category C

625

626 The teratogenic potential of SERDOLECT (sertindole) was studied in Sprague-Dawley
627 rats and New Zealand rabbits dosed during the period of organogenesis. No evidence of
628 a teratogenic effect was detected in rats at doses of 0.1 to 5.0 mg/kg or 0.04 to 2 times
629 the maximum human on a mg/m^2 basis or in rabbits at 0.1 to 3.0 mg/kg or 0.08 to 2.4
630 times the maximum human dose on a mg/m^2 basis.

631

632 In the rat, minor reductions in neonatal bodyweight gain with concomitant delays in
633 maturational indices and altered behavior in treated male offspring (reduced activity)

634 were observed in the neonate only at a maternally toxic dosage level of 4 mg/kg/day (1.6
635 times the maximum human dose on a mg/m² basis). No other developmental effects
636 following *in utero* exposure were observed in the rat.

637

638 In the rabbit study, there were slight increases in total malformations (primarily thoracic
639 and appendicular), visceral anomalies, and skeletal variations in fetuses from does
640 treated at a maternally toxic dosage level of with 3 mg/kg/day (2.4 times the maximum
641 human dose on a mg/m² basis.

642

643 When treatment was extended into the parturition and lactation periods in the peri/post
644 natal study in rats at dose levels of 0.2 to 2 mg/kg/day (or 0.08 to 0.8 times the
645 maximum human dose on a mg/m² basis), there were some indications of effects on
646 parturition, lactation and maternal nursing behavior. This was evidenced by one
647 2 mg/kg/day treated dam being euthanized *in extremis* after 3 days of labor, by lack of
648 milk in some pup stomachs and by the increase in pup deaths in the 0.6 and
649 2 mg/kg/day dosage groups during the early lactation period. Due to signs of maternal
650 toxicity it was not clear whether these deaths were due to a direct effect on the fetuses
651 or pups or to effects on the dams. A no-effect for pup mortality was observed to be
652 0.2 mg/kg/day. Pup weight gain was reduced and delays in sexual maturation (testes
653 decent, vaginal opening) and in performance on a number of developmental tests (eye
654 opening, reflexes) at doses of 0.6 and 2.0 mg/kg or 0.2-0.8 times the maximum human
655 dose on a mg/m² basis were observed. These effects were possibly related to the
656 reduced pup weight. Mating and reproductive performance in the F₁ generation were
657 decreased at 0.2, 0.6 and 2 mg/kg/day.

658

659 There are no adequate and well-controlled studies in pregnant women. SERDOLECT
660 should be used during pregnancy only if the potential benefit justifies the potential risk to
661 the fetus.

662 **8.2 Labor and Delivery**

663 The effect of SERDOLECT on labor and delivery in humans is unknown.

664 **8.3 Nursing Mothers**

665 It is not known whether sertindole or its metabolites are excreted in human milk. Studies
666 in rats indicate that sertindole and/or its metabolites are excreted in rat milk. It is
667 recommended that women receiving SERDOLECT should not breast feed.

668 **8.4 Pediatric Use**

669 The safety and effectiveness of SERDOLECT in individuals below 18 years of age has
670 not been established.

671 **8.5 Geriatric Use**

672 In a study of healthy, elderly subjects (n=28, 65 to 85 years) the pharmacokinetics of
673 SERDOLECT were not significantly different compared to younger adult subjects.
674 Clinical studies of SERDOLECT did not include sufficient numbers of patients over 65
675 years to determine whether they respond differently than younger patients. Slower
676 titration and lower maintenance doses may be appropriate in elderly patients, who
677 potentially may have greater sensitivity to SERDOLECT's pharmacologic effects (see
678 *Clinical Pharmacology and Dosage and Administration*).

679 **8.6 Renal Impairment**

680 The pharmacokinetics of sertindole and dehydrosertindole were similar in patients with
681 renal impairment and normal subjects. In addition, sertindole is not removed by
682 hemodialysis. No dosage adjustment is required in subjects with renal impairment.

683 **8.7 Hepatic Impairment**

684 The clearance of sertindole after a 4 mg oral dose was decreased by about 56% in
685 hepatically impaired patients compared to hepatically normal patients. Patients with mild
686 to moderate hepatic disease require slower titration and a lower maintenance dose.
687 Treatment with SERDOLECT in patients with severe hepatic impairment is
688 contraindicated (see *Dosage and Administration and Contraindications*).

689 **8.8 Gender**

690 The clearance of sertindole is approximately 20% lower in women than in men, but lean-
691 mass corrected clearance is similar. No dosage adjustment is recommended based on
692 gender.

693 **8.9 Race**

694 Pharmacokinetic studies did not demonstrate clinically relevant race-related differences.
695 Population pharmacokinetics analyses revealed that the clearance of sertindole is 20%
696 lower in African-Americans than in Caucasians. No dosage adjustment is recommended
697 based on race.

698 **8.10 Smoking**

699 Population pharmacokinetics analyses of healthy subjects and patients showed that
700 sertindole clearance is about 15% higher in smokers than in non-smokers. No dosage
701 adjustment is recommended based on smoking status.

702
703

704 **9. DRUG ABUSE AND DEPENDENCE**

705 **9.1 Controlled Substance Class**

706 SERDOLECT (sertindole) is not a controlled substance.

707 **9.2 Abuse and Dependence**

708 SERDOLECT has not been systematically studied in animals or humans for its potential
709 for abuse, tolerance or physical dependence. A study of conditioned place preference in
710 rats did not suggest reinforcing properties but rather, inhibition of the effects of
711 morphine, cocaine and metamphetamine has been demonstrated. While the clinical
712 trials did not reveal a tendency for any drug-seeking behavior, these observations were
713 not systematic and it is not possible to predict on the basis of this limited experience the
714 extent to which a CNS-active drug will be misused, diverted and/or abused once
715 marketed. Consequently, patients should be evaluated carefully for a history of drug
716 abuse, and such patients should be observed closely for signs of SERDOLECT misuse
717 or abuse (e.g. development of tolerance, increase in dose, drug-seeking behavior).

718
719

720 **10. OVERDOSAGE**
721

722 **10.1 Human Experience**

723 Experience with SERDOLECT in acute overdose is limited. Fatal cases have occurred.
724 However, a patient taking an estimated dosage of 2000 mg has recovered without
725 sequelae. Reported signs and symptoms of overdose were vomiting, somnolence,
726 slurred speech, tachycardia, hypotension, and transient prolongation of the QTc interval.
727 Cases of Torsade de Pointes have been observed, though confounded in some cases
728 by overdoses of other drugs known to induce Torsade de Pointes.
729

730 **10.2 Management of Overdosage**

731 In case of acute overdosage, establish and maintain an airway and ensure adequate
732 oxygenation and ventilation. Intravenous access should be established and gastric
733 lavage (after intubation, if patient is unconscious) and administration of activated
734 charcoal together with a laxative should be considered. The possibility of obtundation,
735 seizures or dystonic reactions of the head and neck following overdose may create a risk
736 of aspiration with induced emesis.
737

738 Cardiovascular monitoring should commence immediately and should include
739 continuous electrocardiographic monitoring to detect possible arrhythmias. If
740 antiarrhythmic therapy is administered, the QT-prolonging and pro-arrhythmic effects of
741 certain antiarrhythmics should be considered (*see Warnings and Precautions*). If the
742 QTc interval is prolonged, it is recommended that the patient be monitored until the QTc
743 interval has normalized. A half-life of sertindole of 2 to 4 days should be taken into
744 account.
745

746 Hypotension and circulatory collapse should be treated with appropriate measures such
747 as intravenous fluids. If sympathomimetic agents are used for vascular support,
748 epinephrine and dopamine should not be used, since beta stimulation combined with α_1 ,
749 antagonism associated with sertindole may worsen hypotension.
750

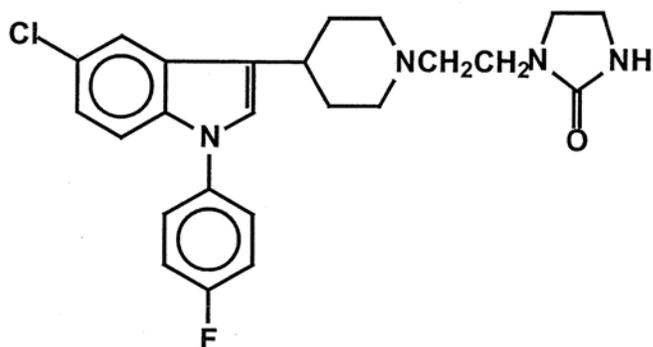
751 In cases of severe extrapyramidal symptoms, anticholinergic medication should be
752 administered.
753

754 There is no specific antidote to sertindole, and it is not dialyzable. The possibility of
755 multiple drug involvement should be considered. Close medical supervision and
756 monitoring should continue until the patient recovers.

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11. DESCRIPTION

SERDOLECT tablets for oral administration contain sertindole, an antipsychotic agent belonging to the class of the phenylindole derivatives. The chemical name is 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]-2ethyl]-2imidazolidinone. Its monocular formula is $C_{24}H_{26}ClFN_4O$ and its molecular weight is 440.9. The structural formula is:



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Sertindole is a white, crystalline material that melts at approximately 165°. It has characteristic infrared and ultraviolet spectra. It is practically insoluble in water. SERDOLECT is available as 4 mg, 12 mg, 16 mg and 20 mg film-coated tablets for oral administration. Inactive ingredients are starch, lactose, hypromellose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. Film coat: Hypromellose, polyethylene glycol, titanium dioxide, iron oxide.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of sertindole, as with other drugs having efficacy in schizophrenia, is unknown. It has been proposed, however, that this drug's efficacy on positive symptoms of schizophrenia is mediated through a combination of dopamine D₂, alpha₁-adrenoceptor and serotonin type 2 (5-HT₂) antagonism, leading to a selective inhibition of limbic versus nigrostriatal dopamine function and thereby predicting efficacy with low potential for induction of extrapyramidal side effects.

12.2 Pharmacodynamics

Sertindole is a monoaminergic antagonist with high affinity (K_i or K_D) for the human serotonin 5-HT_{2A} (0.14 to 0.39 nM), 5-HT_{2C} (0.7 to 6 nM), 5-HT₆ (0.74 nM), human dopamine D₂ subfamily (2.7 to 7.0 nM), D₃ (10 nM), and D₄ subfamily (11 to 21 nM), and human alpha₁-adrenergic (3.9 nM) receptors. Sertindole binds to other receptors but with lower affinity. Sertindole has moderate affinity for the human 5-HT_{1D} (20 to 96 nM), and human dopamine D₁ (510 nM) receptors. Sertindole has weaker affinity for human 5-HT_{1A} (280 to 1050 nM), histamine H₁ (130 to 320 nM), and alpha₂-adrenergic subfamily (190 to 640 nM) receptors. Sertindole has little-to-no affinity for the human cholinergic muscarinic (5000 nM) and beta₁ and beta₂ adrenergic (> 5000 nM) receptors, and rabbit 5-HT₃

795 and rat PCP receptors. The sertindole K_D for human monoamine serotonin,
796 norepinephrine, and dopamine transporters ranges from 200 to 1,200 nM.

797

798 The receptor profile has been confirmed in PET imaging studies in patients with
799 schizophrenia, showing moderate dopamine D_2 receptor occupancies in striatum (Mean
800 60%; Range 52-68 %) at the highest recommended clinical dose (20 mg/day). They are
801 within same range in extrastriatal areas. In addition, 5-HT₂ receptor occupancy has been
802 observed to be fully saturated at a low dose (12 mg/day) in healthy subjects. The low D_2
803 receptor occupancy also provides an explanation for the low risk of extrapyramidal
804 symptoms (EPS) in patients treated with sertindole.

805

806 In preclinical studies it is demonstrated that sertindole can reverse cognitive impairments
807 of working memory and executive function after subchronic treatment with phencyclidine
808 (PCP). There is evidence that 5-HT₆ and, partially, 5-HT_{2A} antagonism mediate the
809 improvement of cognitive function through enhanced dopamine and glutamate function
810 in frontal cortex. Furthermore, sertindole does not induce cognitive deficits in a variety of
811 animal models after acute and subchronic administration, inducing plasma levels
812 exceeding those observed at clinically recommended doses.

813

814 Antagonism at receptors other than dopamine and 5-HT₂ may explain some of the other
815 effects of sertindole, e.g. sertindole's potent antagonism of adrenergic α_1 -adrenoceptors
816 probably explains the orthostatic hypotension and mild tachycardia observed with this
817 drug, as well as decreases in ejaculatory volume.

818

819 The inhibition of the human cardiac hERG potassium channels is considered the
820 underlying mechanism of QT/QTc interval prolongation on the ECG. Sertindole inhibits
821 human cardiac hERG potassium channels in vitro (IC_{50} 3 to 64 nM). Dehydro-sertindole
822 blocks hERG activity with similar potency (IC_{50} 22 nM) and nor-sertindole is 10 fold less
823 potent (IC_{50} = 240 nM). Sertindole and its metabolites, nor-sertindole and dehydro-
824 sertindole, inhibit other human potassium, sodium, and calcium channels with lower
825 potency. However, sertindole shows absence of early after-depolarisations in cardiac
826 rabbit and dog purkinje fibres. Early after-depolarisations are considered essential to
827 trigger Torsade de Pointes ventricular arrhythmia. Sertindole did not induce Torsade de
828 Pointes ventricular arrhythmias in atrio-ventricular node ablated rabbit hearts, despite
829 experimental introduction of severe hypokalaemia (1.5 mmol) and bradycardia.
830 However, the extrapolation of animal findings to humans with regard to QT prolongation
831 and arrhythmia must be undertaken with caution, as significant inter-species differences
832 may exist.

833

834 Sertindole has no effect on muscarinic and histamine H_1 receptors. This is confirmed by
835 the lack of anticholinergic and sedative effects related to those receptors.

836 **12.3 Pharmacokinetics**

837 The clearance of sertindole after multiple doses is around 14 L/h and its mean terminal
838 elimination half-life is approximately 70 hours. Administration of sertindole once daily
839 leads to steady-state concentrations in about 3 weeks. At steady state, clearance is
840 dose independent and trough plasma concentrations are proportional to dose in a range
841 of 4 to 24 mg/day.

842

843

844 **Absorption**

845 Sertindole reaches peak plasma concentrations in approximately 10 hours following an
846 oral dose. Food and aluminum-magnesium antacids have no clinically significant effect
847 on the rate or extent of sertindole absorption.

848

849 **Distribution**

850 Sertindole is extensively distributed throughout the body, having an apparent volume of
851 distribution of approximately 20 L/kg. It is greater than 99% bound to plasma proteins
852 binding primarily to albumin and α_1 -acid glycoprotein. Commonly administered drugs
853 such as salicylates, warfarin, ibuprofen, benzotropine mesylate, propranolol,
854 erythromycin, and terfenadine have no effect on the protein binding of sertindole to
855 human plasma.

856

857 **Metabolism and Elimination**

858 Sertindole is extensively metabolized by the liver. Major pathways of biotransformation
859 are the intermediate hydroxylation step followed by dehydration to form the
860 dehydrosertindole metabolite, present at steady state at 80% of the concentration of
861 sertindole, and cleavage involving N-dealkylation to form the norsertindole metabolite,
862 present at steady state at 40% of the concentrations of sertindole. Sertindole and
863 dehydrosertindole have similar receptor profiles and potencies.

864

865 The principal enzyme involved in the metabolism of sertindole is CYP2D6, with CYP3A
866 appearing to have a lesser role. CYP2D6 is a polymorphic enzyme. About 7% of
867 Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as
868 poor metabolizers (PM). Following dosing with sertindole 8 mg/day for 10 days,
869 sertindole oral clearance in PMs was one-third and elimination half-life 2.5 times that in
870 extensive metabolizers.

871

872 Sertindole and its metabolites are eliminated very slowly, with a total recovery of 52% of
873 a radiolabeled oral dose 14 days after administration. Approximately 4% of the dose is
874 excreted into the urine as parent drug plus metabolites of which less than 1% is present
875 as parent drug. Faecal excretion is the major route of excretion and accounts for the rest
876 of the parent drug and metabolites.

877

878

879 **13. NONCLINICAL TOXICOLOGY**

880 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

881 **Carcinogenesis**

882 Carcinogenicity studies were conducted in CD-1 albino mice and Sprague-Dawley albino
883 rats. Sertindole was administered in the diet to mice at doses of 0.3, 1, 3 and 10 mg/kg
884 for 83-104 weeks and to rats at doses 0.1, 0.5, 1 and 3 mg/kg for 90-96 weeks. These
885 doses are equivalent to 0.06, 0.2, 0.6 and 2 times the maximum human dose (24
886 mg/day) on a mg/m^2 basis (mice) or 0.04, 0.2, 0.4 and 1.2 times the maximum human
887 dose on a mg/m^2 basis (rats). The high dose groups of mice were sacrificed early (week
888 83) due to increased mortality. An increased incidence of hematopoietic lymphomas was
889 detected in male mice receiving 10 mg/kg and in female mice receiving 3 mg/kg (2 and
890 0.6 times the maximum human dose on a mg/m^2 basis). There were statistically
891 significant increases in pituitary gland adenomas in female mice at doses of 1, 3 and 10

892 mg/kg, or 0.2 to 2 times the maximum human dose on the mg/m² basis. There was an
893 increase in mammary gland neoplasms in females but not males of both species. In
894 female mice, there was an increase in mammary gland adenocarcinomas at doses of 1,
895 3 and 10 mg/kg or 0.2 to 2 times the maximum human dose on a mg/m² basis. In female
896 rats, there were increases in mammary gland fibroadenomas and carcinomas at doses
897 of 0.5, 1 and 3 mg/kg or at 0.04 to 1.2 times the maximum human dose on a mg/m²
898 basis. Pancreatic islet cell adenomas and carcinomas were increased in male and
899 female rats at doses of 1 and 3 mg/kg or 0.4 and 1.2 times the maximum human dose
900 on a mg/m² basis.

901

902 Antipsychotic drugs have been shown to increase prolactin levels in rodents. Serum
903 measurements during subchronic toxicity studies showed that sertindole increased
904 serum prolactin levels 4 to 20 fold in female and male mice, respectively, at a dose of 10
905 mg/kg for 4 weeks. In rats, consistent effects on serum prolactin were not demonstrated.
906 In a 7-day dietary study, serum prolactin levels were elevated 5 or 6 fold in male rats at a
907 dose of 6 mg/kg. In a 13-week dietary study in rats, however, no elevations in serum
908 prolactin occurred at doses up to 6 mg/kg. In a 1-year dietary study in rats, consistent
909 elevations in serum prolactin were not demonstrated at doses of 0.1 to 6 mg/kg.
910 Increases in mammary, pituitary and pancreatic islet cell neoplasms have been found in
911 rodents after chronic administration of other antipsychotic drugs and are considered to
912 be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated
913 endocrine tumors in rodents to human risk is unknown (see *Hyperprolactinemia in*
914 *Warnings and Precautions*).

915

916 **Mutagenesis**

917 No evidence of mutagenic or clastogenic potential for sertindole was found in a Ames
918 bacterial reverse mutation assay, a mouse lymphoma assay (gene mutation only), an *in*
919 *vitro* chromosomal aberration test in human lymphocytes, and *in vivo* cytogenetics test in
920 rat bone marrow, or an *in vivo* micronucleus test in mice. Sertindole produced a
921 concentration-related reproducible increase in numerical chromosomal aberrations (i.e.,
922 polyploidy) in the absence or presence of metabolic activation in an *in vitro* assay in
923 human lymphocytes and an *in vivo* rat bone marrow assay.

924

925 **Impairment of Fertility**

926 Sertindole decreased fertility in Sprague-Dawley rats at oral doses of 0.14 and 0.5 mg/kg
927 or 0.06 and 0.2 times the maximum human dose on a mg/m² basis. In subsequent
928 studies in Sprague-Dawley rats, the effect was determined to be male-specific. Drug-
929 related effects included changes in male sexual behavior, and alterations in sperm
930 morphology, motility and count. The no-effect dose for impaired fertility in rats was 0.04
931 mg/kg or 0.02 times the maximum human dose on a mg/m² basis. The effect of
932 sertindole on fertility was also tested in male CD-1 mice. Mating performance was
933 impaired (i.e. increased time to mating decreased number of pregnancies) at oral doses
934 of 1 to 10 mg/kg or 0.2 to 2.0 times the maximum human dose on a mg/m² basis. The
935 no-effect dose was 0.3 mg/kg or 0.06 times the maximum dose on a mg/m² basis.

936

937 Changes in the estrus cycle occurred in rats in a 1-year oral toxicity and in mice in an
938 83-104 week carcinogenicity study. In the rat study, increase in diestrus was observed at
939 doses of 0.75 and 6.0 mg/kg or 0.3 and 2.4 times the maximum human dose on a mg/m²
940 basis. In the mouse study, a decrease in the number of estrus cycles was observed at all
941 doses (0.3-10 mg/kg or 0.06 to 2 times the maximum human dose on a mg/m² basis.)
942 Therefore, the potential for sertindole to impair fertility in humans cannot be excluded.

943 **Binding to Melanin-Containing Tissues**
944 When pigmented rats received a single dose of radiolabelled sertindole, there was
945 evidence for residual binding in the uveal tract after 140 days. Although not directly
946 measured, melanin binding is suggested. While there is a possibility that sertindole could
947 accumulate in melanin-rich tissues such as the eye during extended use, the clinical
948 significance of this finding is unknown.

949
950 **Lens Opacities**
951 In a one-year study in rats sertindole produced anterior suture lens opacities at doses of
952 0.75 and 6 mg/kg/day (0.3 and 2.4 times the maximum human dose on a mg/m² basis).
953 Posterior capsular opacities, cataracts, and patchy hyperreflectivity of the ocular fundus
954 (retina) were reported in mice assessed at week 47 of the carcinogenicity study. Animals
955 receiving doses of 3 and 10 mg/kg/day (0.6 and 2 times the maximum human dose on a
956 mg/m² basis) were affected. The clinical significance of these findings is unknown.
957 However, ophthalmological monitoring in 139 patients during treatment with sertindole in
958 a long-term extension trial did not reveal any unexpected ophthalmological findings (see
959 *Adverse Reactions*).

960
961 **Bone Fragility**
962 In a carcinogenicity study in mice, animals receiving 10 mg/kg/day of sertindole (2 times
963 the maximum human dose on a mg/m² basis) developed hind limb fractures, which were
964 detected by x-ray examination. Although clinical chemistry data suggested some
965 alteration of calcium metabolism (reduced serum calcium, elevated inorganic
966 phosphorous), the underlying mechanism for this effect on bone has not been
967 determined, and clinical significance of these findings is unknown.

968 969 970 **14. CLINICAL STUDIES**

971
972 **Short-term**
973 The efficacy of SERDOLECT in the treatment of schizophrenia was established in a
974 series of studies. Four 6- to 8-week studies were placebo-controlled trials of hospitalized
975 psychotic patients who met DSM III-R or DSM-IV criteria for schizophrenia showed that
976 the symptoms of psychosis are effectively treated with SERDOLECT. Two of the four
977 studies included haloperidol as an active control group but were not designed to allow
978 for a statistical comparison of SERDOLECT and the active control. Five additional
979 studies comparing SERDOLECT with an active-control were also performed. The active
980 controls were haloperidol (three trials) or risperidone (one trial and one prospective
981 study).

982
983 Several instruments were used for assessing psychiatric signs and symptoms in
984 these studies. The Positive and Negative Syndrome Scale (PANSS) is a multi-item
985 inventory of general psychopathology used to evaluate the effect of the drug
986 treatment in schizophrenia. The PANSS positive subscale is a subset of items in the
987 PANSS that rates seven positive symptoms: delusion, conceptual disorganization,
988 hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and
989 hostility. The PANSS negative subscale is a subset of items in the PANSS that rates
990 seven negative symptoms: blunted affect, emotional withdrawal, poor rapport,
991 passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of
992 conversation, and stereotyped thinking. The Brief Psychiatric Rating Scale (BPRS)
993 was also measured in all the studies and is another multi-item inventory of general

994 psychopathology usually used to evaluate the effects of drug treatment in
995 schizophrenia. The Clinical Global Impression (CGI), reflects the impression of a
996 skilled observer, fully familiar with the manifestations of schizophrenia, about the
997 overall clinical state of the patients.

998

999 The results of the SERTINDOLE trials follow:

1000 In an 8-week, placebo-controlled trial involving 3 fixed doses of SERDOLECT (12, 20
1001 and 24 mg/day), 3 fixed doses of haloperidol (4, 8 and 16 mg/day), and placebo, 497
1002 patients were randomized. The change from baseline in the mean total PANSS score
1003 (primary criteria) was statistically significantly improved with all doses of SERDOLECT
1004 compared with placebo. This statistically significant superiority compared with placebo
1005 was also observed for all doses of SERDOLECT in the BPRS and the CGI-severity
1006 score. In addition, the 20 mg and 24 mg doses were statistically significantly superior to
1007 placebo in the PANSS positive subscale. Only the 20 mg dose showed superiority over
1008 placebo in the PANSS negative subscale. The three sertindole doses were clinically and
1009 statistically similar to placebo regarding EPS, as measured by EPS-related adverse
1010 events, use of anti-EPS medication, and movement rating scale scores (AIMS, BAS,
1011 SAS).

1012

1013 In an 8-week, placebo-controlled trial (n=462 randomized) involving 2 fixed doses of
1014 SERDOLECT (20 and 24 mg/day), a single fixed haloperidol dose (16 mg/day), and
1015 placebo, both SERDOLECT doses were statistically significantly superior to placebo on
1016 the PANSS total score (primary criteria), the PANSS positive subscale, the BPRS, and
1017 the CGI-severity score. Only the 24 mg dose showed a statistically significant superiority
1018 over placebo in the PANSS negative subscale. Both sertindole doses were clinically and
1019 statistically similar to placebo regarding EPS, as measured by EPS-related adverse
1020 events, use of anti-EPS medication, and movement rating scale scores (AIMS, BAS,
1021 SAS).

1022

1023 In a 40-day, placebo-controlled trial (n=205 randomized) involving 3 fixed doses of
1024 SERDOLECT (8, 12 and 20 mg/day), and placebo, only the 20 mg dose showed a
1025 statistically significant improvement over placebo in the PANSS total score (primary
1026 criteria) and the BPRS.

1027

1028 In a 7-week, placebo-controlled trial (n=38 randomized), comparing flexible doses of
1029 SERDOLECT between 4 and 20 mg/day and placebo, a statistically significant
1030 improvement compared with placebo was observed in the BPRS (primary criteria) and
1031 the CGI-severity score.

1032

1033 The effective dose range of SERDOLECT in the treatment of schizophrenia was
1034 characterized in an 8-week study (n=617 randomized), which compared four doses of
1035 SERDOLECT (8, 16, 20 and 24 mg/day) and a fixed dose (10 mg/day) of haloperidol in
1036 patients with schizophrenia. A statistically significant monotonic relationship between
1037 increased SERDOLECT dose and increased level of clinical improvement was
1038 demonstrated for the change from baseline on the PANSS total score. The dose of 8 mg
1039 of SERDOLECT was found to be statistically significantly less effective than 16 mg and
1040 24 mg of SERDOLECT and was considered subtherapeutic.

1041

1042 A 12-week double-blind, randomized trial (n=186 randomized) using flexible doses of
1043 SERDOLECT in the range of 12 to 24 mg compared to 4 to 10 mg of risperidone showed
1044 similar efficacy on the PANSS total score, PANSS positive subscale and CGI-severity

1045 score for both compounds but a statistically significantly greater reduction in negative
 1046 symptoms with SERDOLECT.
 1047
 1048 In a 12-week randomized, double-blind trial (n=40 randomized) to compare effects on
 1049 cognitive parameters of SERDOLECT (10 to 24 mg once daily) and haloperidol (5 to 15
 1050 mg once daily) SERDOLECT-treated patients showed less schizophrenia-related
 1051 cognitive disturbances compared to haloperidol-treated patients.
 1052
 1053 In a randomized, active-controlled, open-label, prospective use study (n=9858)
 1054 comparing the safety of SERDOLECT and risperidone, patients treated with
 1055 SERDOLECT had comparable all-cause mortality and a significantly lower risk of fatal or
 1056 non-fatal suicide attempts compared to patients treated with risperidone.
 1057
 1058 **Maintenance**
 1059 The maintenance of the efficacy of Serdolect was confirmed in a 12-month, randomized,
 1060 double-blind, parallel group study (n=282 randomized) comparing SERDOLECT (24
 1061 mg/day) with haloperidol (10 mg/day). Both SERDOLECT-treated and haloperidol-
 1062 treated patients remained stable, showing improvements as determined by time-to-
 1063 treatment-failure, efficacy rating scales and Quality of Life. Haloperidol-treated patients
 1064 had a statistically significantly shorter time to treatment failure due to hospitalization for
 1065 psychotic exacerbation and premature discontinuation for non-compliance compared
 1066 with SERDOLECT-treated patients.
 1067
 1068 Examination of population subsets (race, gender, and age) did not reveal any differential
 1069 responsiveness.

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16. HOW SUPPLIED/STORAGE AND HANDLING

SERDOLECT (sertindole) Tablets have markings on one side and are available in the strengths and packages listed below:

Tablet Strength	Tablet Color/shape	Tablet Markings	Pack Size	NDC Code
4 mg	yellow, oval-biconvex	"S 4"	bottles of 30 or 60 blister of 30 (unit-dose)	
12 mg	beige, oval-biconvex	"S 12"	bottles of 30 or 60 blister of 28 (unit-dose)	
16 mg	red, oval-biconvex	"S 16"	bottles of 30 or 60 blister of 28 (unit-dose)	
20 mg	pink, oval-biconvex	"S 20"	bottles of 30 or 60 blister of 28 (unit-dose)	

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Storage and Handling:

Store tablets at controlled room temperature 15-30°C (59-86°F). Protect from light and moisture.
Keep out of reach of children.

Rx only

1085
1086
1087
1088

17. PATIENT COUNSELING INFORMATION

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1090

Physicians are advised to discuss the following issues with patients for whom they prescribe SERDOLECT.

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1097

17.1 Elderly Patients with Dementia-related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. SERDOLECT is not approved for elderly patients with dementia-related psychosis (*see Warnings and Precautions*).

17.2 QT Prolongation

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Patients, their families and their caregivers should be encouraged to be alert to the emergence of certain symptoms; in particular dizziness, palpitations, and syncope that could be related to sertindole-induced QT prolongation. Patients should inform their physicians if such events occur (*see Warnings and Precautions*).

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1106

17.3 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration, and provided advice on how to avoid orthostatic hypotension and what to do if it occurs.

1107

17.4 Interference with Cognitive and Motor Performance

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1109
1110
1111

Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SERDOLECT therapy does not affect them adversely. SERDOLECT was not distinguishable from placebo with regards to the occurrence of somnolence in short-term studies.

1112

17.5 Diabetes

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1114
1115

Antipsychotic medications as a class have been associated with decreased glucose tolerance. Diabetic patients treated with SERDOLECT may find that their need for antidiabetic medications is altered while on medication.

1116

17.6 Decreased Ejaculatory Volume

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Male patients may experience decreased ejaculatory volume. Patients in clinical trials have described either absent or reduced volume of ejaculate, generally associated with normal libido, erection and orgasm. Patients with decreased ejaculatory volume do produce sperm and should be advised to use appropriate contraceptive measures to avoid unwanted pregnancy.

- 1122 **17.7 Pregnancy**
1123 Patients should be advised to notify their physician if they become pregnant or intend to
1124 become pregnant during therapy.
- 1125 **17.8 Nursing**
1126 Patients should be advised not to breast feed an infant if they are taking SERDOLECT.
- 1127 **17.9 Concomitant Medication**
1128 Patients should be advised to inform their physicians if they are taking, or plan to take,
1129 any prescription drugs, since there is a potential for interactions.
1130
- 1131 **17.10 Alcohol**
1132 Patients should be advised to avoid alcohol while taking Serdolect.
1133
- 1134 **17.11 Heat Exposure and Dehydration**
1135 Patients should be advised regarding appropriate care in avoiding overheating and
1136 dehydration.
1137
- 1138 **Manufactured by:**
1139 H. Lundbeck A/S
1140 Denmark
1141
1142