
Professional information

1 **SCHEDULING STATUS:** S5

2

3 **PROPRIETARY NAME AND DOSAGE FORM:**

4 MOLIPAXIN 50 mg Capsules

5 MOLIPAXIN 100 mg Capsules

6

7 **COMPOSITION:**

8 MOLIPAXIN 50 mg capsule: trazodone hydrochloride 50 mg.

9 MOLIPAXIN 100 mg capsule: trazodone hydrochloride 100 mg.

10 Other ingredients include lactose monohydrate, magnesium stearate, gelatin, erythrosine E127,
11 indigo carmine E132, titanium dioxide E171 and yellow iron oxide E172, ink 0619 (S-1-20952).

12 The 100 mg MOLIPAXIN capsules also contain Red Iron Oxide (E172).

13 Contains sugar (lactose).

14

15 **PHARMACOLOGICAL CLASSIFICATION:**

16 A 1.2 Psychoanaleptics (antidepressants)

17

18 **PHARMACOLOGICAL ACTION:**

19 **Pharmacodynamic properties**

20 Trazodone hydrochloride is a triazolopyridine derivative chemically unrelated to known tricyclic,
21 tetracyclic and other antidepressant agents. It has negligible effect on norepinephrine
22 (noradrenaline) re-uptake mechanisms. Whilst the mode of action of MOLIPAXIN is not known
23 precisely, its antidepressant activity may concern norepinephric potentiation by mechanisms other
24 than uptake blockade. A central antiserotonin effect may account for the anxiety reducing
25 properties of trazodone.

26 Trazodone hydrochloride is an anxiolytic/antidepressant, psychotropic agent.

27 **Pharmacokinetic properties:**

28 Trazodone is rapidly absorbed from the gastrointestinal tract and extensively metabolised in the
29 liver. Paths of metabolism of trazodone include n-oxidation and hydroxylation. Trazodone is
30 metabolised to its active metabolite m-chlorophenylpiperazine via the cytochrome P450
31 isoenzyme CYP3A4.

32 Trazodone is excreted in the urine almost entirely in the form of its metabolites, either in free or in
33 conjugated form. The elimination of trazodone is biphasic, with a terminal elimination half-life of 5
34 to 13 hours. Trazodone is excreted in breast milk.

35 There was an approximate two-fold increase in terminal phase half-life and significantly higher
36 plasma concentrations of trazodone in 10 subjects aged 65 to 74 years compared with 12
37 subjects aged 23 to 30 years following a 100 mg dose of trazodone. It was suggested that there is
38 an age-related reduction in the hepatic metabolism of trazodone.

39

40 **INDICATIONS:**

41 MOLIPAXIN is indicated in the treatment of depression and mixed anxiety and depression.

42

43 **CONTRAINDICATIONS:**

- 44 • Known hypersensitivity to trazodone or to any of the excipients of MOLIPAXIN.
- 45 • Combined use with other psychotropic medicines should only be undertaken with due
46 recognition of the possibility of potentiation (see INTERACTIONS).
- 47 • Concurrent administration with monoamine oxidase inhibitors (MAOIs), or within two weeks of
48 stopping treatment with these compounds. Administration of MAOIs within one week of
49 stopping MOLIPAXIN.
- 50 • Alcohol intoxication and intoxication with hypnotics.

- 51 • Acute myocardial infarction (see WARNINGS AND SPECIAL PRECAUTIONS).

52

53 **WARNINGS AND SPECIAL PRECAUTIONS:**

54 **Use in children and adolescents under 18 years of age:**

55 MOLIPAXIN should not be used in children and adolescents under 18 years of age. Suicidal
56 behaviour (suicidal attempt and suicidal planning) and hostility (essentially aggressiveness,
57 opposing behaviour and anger) has been observed in clinical studies on children and adolescents
58 treated with antidepressant more frequently than with placebo. Moreover, long-term safety data
59 on children and adolescents regarding growth, maturation and cognitive and behavioural
60 development are not available.

61

62 **Suicide/suicidal thoughts or clinical worsening:**

63 Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide
64 (suicide-related events). This risk persists until significant remission occurs. As improvement may
65 not occur during the first few weeks or more of treatment, patients should be closely monitored
66 until such improvement occurs. It is general clinical experience that the risk of suicide may
67 increase in the early stages of recovery.

68

69 Other psychiatric conditions for which MOLIPAXIN is prescribed may also be associated with an
70 increased risk of suicide-related events. In addition, these conditions may be co-morbid with major
71 depressive disorder. The same precautions observed when treating patients with major
72 depressive disorder should therefore be observed when treating patients with other psychiatric
73 disorders.

74

75 Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal
76 ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts
77 or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of
78 placebo-controlled clinical trials of antidepressant medication in adult patients with psychiatric
79 disorders showed an increased risk of suicidal behaviour with antidepressants compared to
80 placebo in patients less than 25 years old.

81

82 Close supervision of patients and in particular those at high risk should accompany MOLIPAXIN
83 therapy especially in early treatment and following dose changes. Patients (and caregivers of
84 patients) should be alerted about the need to monitor for any clinical worsening, suicidal
85 behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately
86 if these symptoms present.

87

88 To minimise the potential risk of suicide attempts, particularly at therapy initiation, only restricted
89 quantities of MOLIPAXIN should be prescribed at each occasion.

90

91 MOLIPAXIN should be administered with care and regular monitoring should be adopted in
92 patients with the following conditions:

- 93 • epilepsy, avoiding in particular, abrupt increases or decreases in dosage (see
94 INTERACTIONS)
- 95 • hepatic or renal impairment, particularly if severe
- 96 • cardiac disease, such as angina pectoris, conduction disorders or AV blocks of different
97 degree and its use is not recommended in the immediate recovery phase after myocardial
98 infarction (see CONTRAINDICATIONS)
- 99 • hyperthyroidism

- 100 • micturition disorders, such as prostate hypertrophy
- 101 • acute narrow angle glaucoma, raised intra-ocular pressure.

102

103 MOLIPAXIN should be stopped immediately if patients develop signs of hepatic dysfunction, or
104 blood dyscrasias.

105

106 Severe hepatic disorders with potential fatal outcome have been reported with MOLIPAXIN use
107 (see SIDE EFFECTS). Patients should be instructed to report immediately signs such as
108 asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a doctor or healthcare
109 professional. Investigations including clinical examination and biological assessment of liver
110 function should be undertaken immediately, and withdrawal of MOLIPAXIN initiated.

111

112 Since agranulocytosis may clinically reveal itself with influenza-like symptoms, sore throat, and
113 fever, in these cases it is recommended to check haematology.

114

115 Administration of antidepressants in patients with schizophrenia or other psychotic disorders may
116 result in a worsening of psychotic symptoms. Paranoid thoughts may be intensified. During
117 therapy with MOLIPAXIN a depressive phase can change from a manic – depressive psychosis
118 into a manic phase. In that case MOLIPAXIN must be stopped.

119

120 Interactions in terms of serotonin syndrome/malignant neuroleptic syndrome have been described
121 in case of concomitant use of other serotonergically acting substances like other antidepressants
122 (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI's), serotonin and
123 norepinephrine reuptake inhibitors (SNRI's), MAOIs and neuroleptics (see SIDE EFFECTS).

124 Malignant neuroleptic syndromes with fatal outcome have been reported in cases of co-
125 administration with neuroleptics, for which this syndrome is a known possible side effect.

126

127 Hypotension, including orthostatic hypotension and syncope, has occurred in patients receiving
128 MOLIPAXIN. Concomitant administration of antihypertensive therapy with MOLIPAXIN may
129 require a reduction in the dose of the antihypertensive medicine.

130

131 Elderly patients are often more sensitive to antidepressants, in particular to orthostatic
132 hypotension and other anticholinergic effects.

133

134 Following therapy with MOLIPAXIN, particularly for a prolonged period, an incremental dosage
135 reduction to withdrawal is recommended, to minimise the occurrence of withdrawal symptoms,
136 characterised by nausea, headache, and malaise.

137

138 Cases of QT interval prolongation have been reported with MOLIPAXIN less frequently. Caution is
139 advised when prescribing MOLIPAXIN with medicinal products known to prolong the QT interval.

140 MOLIPAXIN should be used with caution in patients with known cardiovascular disease including
141 those associated with prolongation of the QT interval (see INTERACTIONS).

142

143 MOLIPAXIN should be administered with care to patients receiving barbiturates, muscle relaxants
144 and volatile anaesthetics, since it has been shown to potentiate the action of these substances.

145

146 Potent CYP3A4 inhibitors may lead to increases in MOLIPAXIN serum levels (see
147 INTERACTIONS).

148

149 MOLIPAXIN has less frequently been associated with priapism. This may be treated with an
150 intracavernosum injection of an alpha-adrenergic agent such as epinephrine (adrenaline) or
151 metaraminol. However there are reports of MOLIPAXIN-induced priapism which have required
152 surgical intervention or led to permanent sexual dysfunction. Patients developing inappropriate or
153 prolonged penile erections should stop the use of MOLIPAXIN immediately.

154

155 MOLIPAXIN contains lactose which may have an effect on the glycaemic control of patients with
156 diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance e.g.
157 galactosaemia, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take
158 MOLIPAXIN.

159

160 **Effects on ability to drive and use machines:**

161 Patients should be warned about the possibility of their judgement being impaired by drowsiness,
162 sedation, dizziness, confusional states, or blurred vision when operating dangerous machinery
163 and when driving.

164

165

166

167 **INTERACTIONS:**

168 **Alcohol:** MOLIPAXIN intensifies the sedative effects of alcohol. Alcohol should be avoided
169 during MOLIPAXIN therapy (see CONTRAINDICATIONS).

170

171 **Tricyclic antidepressants:** Concurrent administration should be avoided due to the risk of
172 interaction. Serotonin syndrome and cardiovascular side effects should be beware of (see
173 WARNINGS AND SPECIAL PRECAUTIONS).

174

175 **Fluoxetine:** Less frequent cases have been reported of elevated trazodone plasma levels and
176 adverse effects when MOLIPAXIN had been combined with fluoxetine, a CYP1A2/2D6 inhibitor.
177 The mechanism underlying a pharmacokinetic interaction is not fully understood. A
178 pharmacodynamic interaction (serotonin syndrome) could not be excluded.

179 The concurrent use of tricyclic or related antidepressants and lithium may promote neurotoxic side
180 effects.

181

182 **CYP3A4 inhibitors:** In vitro medicine metabolism studies suggest that there is a potential for
183 medicine interactions when MOLIPAXIN is given with potent CYP3A4 inhibitors such as
184 erythromycin, ketoconazole, itraconazole, ritonavir, indinavir, and nefazodone. It is likely that
185 potent CYP3A4 inhibitors may lead to substantial increases in MOLIPAXIN plasma concentrations
186 with the potential for adverse effects. Exposure to ritonavir during initiation or resumption of
187 treatment in patients receiving MOLIPAXIN will increase the potential for excessive sedation,
188 cardiovascular, and gastrointestinal effects. If MOLIPAXIN is used with a potent CYP3A4 inhibitor,
189 a lower dose of MOLIPAXIN should be considered. However, the co-administration of
190 MOLIPAXIN and potent CYP3A4 inhibitors should be avoided where possible.

191

192 **General:** The sedative effects of antipsychotics, hypnotics, sedatives, anxiolytics, and
193 antihistaminic medicines may be intensified; dosage reduction is recommended in such instances
194 (see CONTRAINDICATIONS).

195 The metabolism of antidepressants is accelerated due to hepatic effects by oral contraceptives,
196 phenytoin, carbamazepine and barbiturates. The metabolism of antidepressants is inhibited by
197 cimetidine and some other antipsychotics.

198

199 **Carbamazepine:** Carbamazepine reduced plasma concentrations of MOLIPAXIN when co-
200 administered. Patients should be closely monitored to see if there is a need for an increased dose
201 of MOLIPAXIN when treated concomitantly with carbamazepine.

202

203 **Anaesthetics/muscle relaxants:** MOLIPAXIN may enhance the effects of muscle relaxants and
204 volatile anaesthetics. Antidepressants may accelerate the metabolism of levodopa.

205

206 **Phenothiazines:** Severe orthostatic hypotension has been observed in case of concomitant use
207 of phenothiazines such as chlorpromazine (see WARNINGS AND SPECIAL PRECAUTIONS).

208

209 **Other:** Since MOLIPAXIN is only a very weak inhibitor of noradrenaline re-uptake and does not
210 modify the blood pressure response to tyramine, interference with the hypotensive action of
211 guanethidine-like compounds is unlikely. However, studies in laboratory animals suggest that
212 MOLIPAXIN may inhibit most of the acute actions of clonidine. In the case of other types of
213 antihypertensive medicines, the possibility of potentiation should be considered.

214

215 Concomitant use of apraclonidine or brimonidine and MOLIPAXIN is not recommended.

216

217 Concomitant use of MOLIPAXIN with the anti-dysrhythmic medicine amiodarone or other
218 medicines known to prolong the QT interval may increase the risk of ventricular dysrhythmias,
219 including Torsade de Pointes. Caution should be used when these medicines are co-administered
220 with MOLIPAXIN.

221

222 Concurrent use with MOLIPAXIN may result in elevated serum levels of digoxin or phenytoin.

223 Monitoring of serum levels should be considered in these patients. In general, antidepressants

224 may antagonise the anti-convulsant effect of anti-epileptics by lowering the seizure threshold (see
225 WARNINGS AND SPECIAL PRECAUTION).

226

227 **Warfarin:** Increases and decreases in INR/prothrombin time have been reported in patients
228 concomitantly receiving MOLIPAXIN and warfarin. Therefore it is prudent to monitor the INR in
229 patients taking warfarin, when treatment with MOLIPAXIN is started or stopped, and adjusting the
230 warfarin dose if necessary.

231

232 **Tryptophan:** Since both MOLIPAXIN and tryptophan lead to an increase in 5-HT level at the
233 synapse via different mechanisms of action, there is a possibility of a pharmacodynamic
234 interaction which may lead to serotonin syndrome.

235

236 Undesirable effects may be more frequent when MOLIPAXIN is administered together with
237 preparations containing *Hypericum perforatum* (St John's Wort).

238

239

240

241 **HUMAN REPRODUCTION:**

242 **Pregnancy:**

243 The safety of MOLIPAXIN in pregnancy and breastfeeding has not been established.

244 **Lactation:**

245 MOLIPAXIN is excreted in the breastmilk and may have an effect on the breastfeeding infant.

246 Mothers on treatment with MOLIPAXIN should not breastfeed their infants.

247

248 **DOSAGE AND DIRECTIONS FOR USE:**

249 The dosage is dependent upon the diagnosis and the severity of the condition and the individual
250 patient's response. The daily dosage is usually administered in three divided doses.

251

252 **Adults:**

253 **Depression:** The optimal dosage is between 300 - 400 mg/day. It is suggested that a starting
254 dose of 150 mg/day is given for the first week, increasing to 300 mg/day – 400 mg/day according
255 to the clinical response. The dose may be further increased to 600 mg/day in divided doses in
256 hospitalised patients.

257 **Mixed anxiety and depression:** The recommended starting dose is between 100 – 150 mg/day.
258 When depression is the predominant symptom, a dose of 300 – 400 mg daily may be required to
259 obtain a satisfactory response.

260 **Children and adolescents under 18 years of age:**

261 MOLIPAXIN is not recommended for use in children and adolescents under 18 years of age.

262 **Elderly:**

263 For very elderly or frail patients the recommended initial starting dose is reduced to 100 mg/day
264 given in divided doses or as a single night-time dose. This may be incrementally increased, under
265 supervision, according to efficacy and tolerance. In general, single doses above 100 mg should
266 be avoided in these patients. It is unlikely that 300 mg/day will be exceeded.

267

268 **SIDE EFFECTS:**

269 The following side effects have been reported and the frequencies have been indicated where
270 known.

271 **Blood and lymphatic system disorders:**

272 *Less frequent:* blood dyscrasias, including agranulocytosis, thrombocytopenia, anaemia (see

273 WARNINGS AND SPECIAL PRECAUTIONS)

274 *Frequency unknown:* eosinophilia, leucopenia

275 **Immune system disorders:**

276 *Frequency unknown:* allergic reactions

277 **Endocrine disorders:**

278 *Frequency unknown:* Syndrome of Inappropriate Antidiuretic Hormone Secretion

279 **Metabolism and nutrition disorders:**

280 *Frequency unknown:* hyponatraemia*, weight loss, anorexia, increased appetite

281 * Fluid and electrolyte status should be monitored in symptomatic patients

282 **Psychiatric disorders:**

283 *Frequent:* confusional states

284 *Frequency unknown:* suicidal ideation or suicidal behaviours (see WARNINGS AND SPECIAL
285 PRECAUTIONS), insomnia, disorientation, mania, anxiety, nervousness, agitation (less frequently
286 exacerbating to delirium), delusion, aggressive reaction, hallucinations, nightmares, libido
287 decreased, withdrawal syndrome

288 **Nervous system disorders:**

289 *Frequent:* headache, dizziness, drowsiness, tremor, excitement

290 *Frequency unknown:* vertigo, decreased alertness, restlessness, irritability, memory disturbance,
291 expressive aphasia, dystonia, taste altered, paraesthesia, myoclonus

292

293 There have been reports of serotonin syndrome and convulsions associated with the use of
294 MOLIPAXIN (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS), especially
295 when associated with other psychotropic medicines. Neuroleptic malignant syndrome has been
296 reported

297 **Eye disorders:**

298 *Less frequent:* blurred vision

299 **Cardiac disorders:**

300 *Less frequent:* bradycardia or tachycardia

301 *Frequencies unknown:* Clinical studies in patients with pre-existing cardiac disease indicate that
302 MOLIPAXIN may be dysrhythmogenic in some patients in that population. Dysrhythmias identified
303 include Torsade de Pointes, palpitations, premature ventricular contractions, ventricular couplets,
304 short episodes (3-4 beats) of ventricular tachycardia and ECG abnormalities (QT prolongation)
305 (see WARNINGS AND SPECIAL PRECAUTIONS).

306 **Vascular disorders:**

307 *Less frequent:* orthostatic hypotension

308 *Frequency unknown:* hypertension, syncope

309 **Respiratory, thoracic and mediastinal disorders:**

310 *Frequency unknown:* nasal congestion, dyspnoea

311 **Gastrointestinal disorders:**

312 *Frequent:* nausea, vomiting, dry mouth

313 *Less frequent:* constipation, diarrhoea

314 *Frequency unknown:* dyspepsia, increased salivation, stomach pain, gastroenteritis, paralytic ileus

315 **Hepato-biliary disorders:**

316 *Frequency unknown:* severe hepatic disorders such as hepatitis/fulminant hepatitis, hepatic failure
317 with potential fatal outcome, cholestasis intrahepatic. Should adverse effects on hepatic function,
318 including jaundice and hepatocellular damage occur, MOLIPAXIN should be discontinued
319 immediately (see WARNINGS AND SPECIAL PRECAUTION).

320 **Skin and subcutaneous tissue disorders:**

321 *Less frequent:* skin rashes

322 *Frequency unknown:* hyperhidrosis, pruritus

323 **Musculoskeletal and connective tissue disorders:**

324 *Frequency unknown:* pain in limb, back pain, myalgia, arthralgia

325 **Renal and urinary disorders:**

326 *Frequency unknown:* micturition disorder

327 **Reproductive system and breast disorders:**

328 *Less frequent:* priapism (see WARNINGS AND SPECIAL PRECAUTIONS)

329 **General disorders and administration site conditions:**

330 *Less frequent:* weakness

331 *Frequency unknown:* oedema, influenza-like symptoms, chest pain, fatigue, fever

332 **Investigations:**

333 *Frequency unknown:* elevated liver enzymes

334

335 **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

336 The most frequently reported reactions to overdose have included drowsiness, dizziness, nausea
337 and vomiting. In more serious cases coma, tachycardia, hypotension, hyponatraemia, convulsions

338 and respiratory failure have been reported. Cardiac features may include bradycardia, QT

339 prolongation and Torsade de Pointes. Symptoms may appear 24 hours or more after overdose.

340 Overdoses of MOLIPAXIN in combination with other antidepressants may cause serotonin
341 syndrome.

342 **Management:**

343 There is no specific antidote to MOLIPAXIN. The stomach should be emptied as quickly as
344 possible and symptomatic and supportive therapy given.

345

346 **IDENTIFICATION:**

347 MOLIPAXIN 50 mg Capsules: Opaque, violet cap and opaque, green body with R365B printed on
348 one half and the company logo on the other half; containing a white powder.

349 MOLIPAXIN 100 mg Capsules: Opaque, violet cap and opaque, fawn body with R365C printed on
350 one half and the company logo on the other half; containing a white powder.

351

352 **PRESENTATION:**

353 MOLIPAXIN capsules (all strengths) are presented in clear PVDC coated PVC/aluminium blister
354 packs each containing 20 capsules. The 50 mg and 100 mg capsules are packed in cartons of
355 100 capsules.

356

357 **STORAGE INSTRUCTIONS:**

358 Store in a cool, dry place, at or below 30 °C.
359 Protect from light. Keep blister in carton until required for use.

360 KEEP OUT OF REACH OF CHILDREN.

361

362

363

364 **REGISTRATION NUMBERS:**

365 MOLIPAXIN 50 mg capsules: E/1.2/9

366 MOLIPAXIN 100 mg capsules: E/1.2/10

367

368 **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF**

369 **REGISTRATION:**

370 sanofi-aventis south africa (pty) ltd

371 2 Bond Street,

372 Midrand

373 1685

374 South Africa

375

376 **DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

377 Date registered: 27 April 1981

378 Date revised: 05 February 2019 (SR-PIN)

379

380

NAMIBIA

381

Scheduling status: NS3

382

Registration numbers:

383

Molipaxin 50 mg Capsule: 90/1.2/00326

384

Molipaxin 100 mg Capsule: 90/1.2/00325