

PRESCRIBING INFORMATION

PARNATE[®]
(tranylcypromine sulfate)
tablets 10 mg

Suicidality and Antidepressant Drugs

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

DESCRIPTION

Chemically, tranylcypromine sulfate is (\pm)-*trans*-2-phenylcyclopropylamine sulfate (2:1). Each round, rose-red, film-coated tablet is debossed with the product name PARNATE and SB and contains tranylcypromine sulfate equivalent to 10 mg of tranylcypromine. Inactive ingredients consist of cellulose, citric acid, croscarmellose sodium, D&C Red No. 7, FD&C Blue No. 2, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, talc, titanium dioxide, and trace amounts of other inactive ingredients.

ACTION

Tranylcypromine is a non-hydrazine monoamine oxidase inhibitor with a rapid onset of activity. It increases the concentration of epinephrine, norepinephrine, and serotonin in storage sites throughout the nervous system and, in theory, this increased concentration of monoamines in the brain stem is the basis for its antidepressant activity. When tranylcypromine is withdrawn, monoamine oxidase activity is recovered in 3 to 5 days, although the drug is excreted in 24 hours.

INDICATIONS

For the treatment of Major Depressive Episode Without Melancholia.

22 PARNATE should be used in adult patients who can be closely supervised. It should rarely be
23 the first antidepressant drug given. Rather, the drug is suited for patients who have failed to
24 respond to the drugs more commonly administered for depression.

25 The effectiveness of PARNATE has been established in adult outpatients, most of whom had
26 a depressive illness which would correspond to a diagnosis of Major Depressive Episode
27 Without Melancholia. As described in the American Psychiatric Association's Diagnostic and
28 Statistical Manual, third edition (DSM III), Major Depressive Episode implies a prominent and
29 relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that
30 usually interferes with daily functioning and includes at least 4 of the following 8 symptoms:
31 change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual
32 activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness,
33 slowed thinking or impaired concentration, and suicidal ideation or attempts.

34 The effectiveness of PARNATE in patients who meet the criteria for Major Depressive
35 Episode with Melancholia (endogenous features) has not been established.

36 **SUMMARY OF CONTRAINDICATIONS**

37 PARNATE should not be administered in combination with any of the following: MAO
38 inhibitors or dibenzazepine derivatives; sympathomimetics (including amphetamines); some
39 central nervous system depressants (including narcotics and alcohol); antihypertensive, diuretic,
40 antihistaminic, sedative, or anesthetic drugs; bupropion HCl; buspirone HCl; dextromethorphan;
41 cheese or other foods with a high tyramine content; or excessive quantities of caffeine.

42 **PARNATE should not be administered to any patient with a confirmed or suspected**
43 **cerebrovascular defect or to any patient with cardiovascular disease, hypertension, or**
44 **history of headache.**

45 (For complete discussion of contraindications and warnings, see below.)

46 **CONTRAINDICATIONS**

47 **PARNATE is contraindicated:**

48 **1. In patients with cerebrovascular defects or cardiovascular disorders**

49 PARNATE should not be administered to any patient with a confirmed or suspected
50 cerebrovascular defect or to any patient with cardiovascular disease or hypertension.

51 **2. In the presence of pheochromocytoma**

52 PARNATE should not be used in the presence of pheochromocytoma since such tumors
53 secrete pressor substances.

54 **3. In combination with MAO inhibitors or with dibenzazepine-related entities**

55 PARNATE should not be administered together or in rapid succession with other MAO
56 inhibitors or with dibenzazepine-related entities. Hypertensive crises or severe convulsive
57 seizures may occur in patients receiving such combinations.

58 In patients being transferred to PARNATE from another MAO inhibitor or from a
59 dibenzazepine-related entity, allow a medication-free interval of at least a week, then initiate
60 PARNATE using half the normal starting dosage for at least the first week of therapy. Similarly,
61 at least a week should elapse between the discontinuance of PARNATE and the administration

62 of another MAO inhibitor or a dibenzazepine-related entity, or the readministration of
63 PARNATE.

64 The following list includes some other MAO inhibitors, dibenzazepine-related entities and
65 tricyclic antidepressants, and the companies which market them.

66 **Other MAO Inhibitors**

Generic Name	Source
Furazolidone	
Isocarboxazid	Marplan [®] (Oxford Pharm Services)
Pargyline HCl	
Pargyline HCl and methyclothiazide	
Phenelzine sulfate	Nardil [®] (Pfizer)
Procarbazine HCl	Matulane [®] (Sigma Tau)

67 **Dibenzazepine-Related and Other Tricyclics**

Generic Name	Source
Amitriptyline HCl	(Sandoz)
Perphenazine and amitriptyline HCl	(Sandoz)
Clomipramine hydrochloride	Anafranil [®] (Mallinckrodt)
Desipramine HCl	(Sandoz)
Imipramine HCl	(Sandoz)
	Tofranil [®] (Mallinckrodt)
Nortriptyline HCl	(Mylan)
	Pamelor [®] (Mallinckrodt)
Protriptyline HCl	Vivactil [®] (Odyssey Pharmaceuticals, Inc.)
Doxepin HCl	Sinequan [®] (Pfizer)
Carbamazepine	Tegretol [®] (Novartis)
Cyclobenzaprine HCl	(Mylan)
	Flexeril [®] (McNeil)
Amoxapine	(Watson)
Maprotiline HCl	(Mylan)
Trimipramine maleate	Surmontil [®] (Odyssey Pharmaceuticals, Inc.)

68 **4. In combination with bupropion**

69 The concurrent administration of an MAO inhibitor and bupropion hydrochloride
70 (Wellbutrin[®], Wellbutrin SR[®], Wellbutrin XL[®], Zyban[®], GlaxoSmithKline) is contraindicated.
71 At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of
72 treatment with bupropion hydrochloride.

73 **5. In combination with dexfenfluramine hydrochloride**

74 Because dexfenfluramine hydrochloride is a serotonin releaser and reuptake inhibitor, it
75 should not be used concomitantly with PARNATE.

76 **6. In combination with selective serotonin reuptake inhibitors (SSRIs)**

77 As a general rule, PARNATE should not be administered in combination with any SSRI.
78 There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity,
79 myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental
80 status changes that include extreme agitation progressing to delirium and coma) in patients
81 receiving fluoxetine (Prozac[®], Eli Lilly and Company) in combination with a monoamine

82 oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are
83 then started on an MAOI. Some cases presented with features resembling neuroleptic malignant
84 syndrome. Therefore, fluoxetine and other SSRIs should not be used in combination with an
85 MAOI, or within 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major
86 metabolite have very long elimination half-lives, at least 5 weeks should be allowed after
87 stopping fluoxetine before starting an MAOI.

88 At least 2 weeks should be allowed after stopping sertraline (Zoloft[®], Pfizer) or paroxetine
89 (Paxil[®], GlaxoSmithKline) before starting an MAOI.

90 **7. In combination with bupirone**

91 PARNATE should not be used in combination with bupirone HCl, since several cases of
92 elevated blood pressure have been reported in patients taking MAO inhibitors who were then
93 given bupirone HCl. At least 10 days should elapse between the discontinuation of PARNATE
94 and the institution of bupirone HCl.

95 **8. In combination with sympathomimetics**

96 PARNATE should not be administered in combination with sympathomimetics, including
97 amphetamines, and over-the-counter drugs such as cold, hay fever or weight-reducing
98 preparations that contain vasoconstrictors.

99 During therapy with PARNATE, it appears that certain patients are particularly vulnerable to
100 the effects of sympathomimetics when the activity of certain enzymes is inhibited. Use of
101 sympathomimetics and compounds such as guanethidine, methyl dopa, reserpine, dopamine,
102 levodopa, and tryptophan with PARNATE may precipitate hypertension, headache, and related
103 symptoms. The combination of MAOIs and tryptophan has been reported to cause behavioral
104 and neurologic syndromes including disorientation, confusion, amnesia, delirium, agitation,
105 hypomanic signs, ataxia, myoclonus, hyperreflexia, shivering, ocular oscillations, and Babinski's
106 signs.

107 **9. In combination with meperidine**

108 Do not use meperidine concomitantly with MAO inhibitors or within 2 or 3 weeks following
109 MAOI therapy. Serious reactions have been precipitated with concomitant use, including coma,
110 severe hypertension or hypotension, severe respiratory depression, convulsions, malignant
111 hyperpyrexia, excitation, peripheral vascular collapse, and death. It is thought that these reactions
112 may be mediated by accumulation of 5-HT (serotonin) consequent to MAO inhibition.

113 **10. In combination with dextromethorphan**

114 The combination of MAO inhibitors and dextromethorphan has been reported to cause brief
115 episodes of psychosis or bizarre behavior.

116 **11. In combination with cheese or other foods with a high tyramine content**

117 Hypertensive crises have sometimes occurred during therapy with PARNATE after ingestion
118 of foods with a high tyramine content. In general, the patient should avoid protein foods in which
119 aging or protein breakdown is used to increase flavor. In particular, patients should be instructed
120 not to take foods such as cheese (particularly strong or aged varieties), sour cream, Chianti wine,
121 sherry, beer (including nonalcoholic beer), liqueurs, pickled herring, anchovies, caviar, liver,
122 canned figs, dried fruits (raisins, prunes, etc.), bananas, raspberries, avocados, overripe fruit,
123 chocolate, soy sauce, sauerkraut, the pods of broad beans (fava beans), yeast extracts, yogurt,
124 meat extracts, or meat prepared with tenderizers.

125 **12. In patients undergoing elective surgery**

126 Patients taking PARNATE should not undergo elective surgery requiring general anesthesia.
127 Also, they should not be given cocaine or local anesthesia containing sympathomimetic
128 vasoconstrictors. The possible combined hypotensive effects of PARNATE and spinal anesthesia
129 should be kept in mind. PARNATE should be discontinued at least 10 days prior to elective
130 surgery.

131 **ADDITIONAL CONTRAINDICATIONS**

132 In general, the physician should bear in mind the possibility of a lowered margin of safety
133 when PARNATE is administered in combination with potent drugs.

- 134 1. PARNATE should not be used in combination with some central nervous system depressants
135 such as narcotics and alcohol, or with hypotensive agents. A marked potentiating effect on these
136 classes of drugs has been reported.
- 137 2. Anti-parkinsonism drugs should be used with caution in patients receiving PARNATE since
138 severe reactions have been reported.
- 139 3. PARNATE should not be used in patients with a history of liver disease or in those with
140 abnormal liver function tests.
- 141 4. Excessive use of caffeine in any form should be avoided in patients receiving PARNATE.

142 **WARNINGS TO PHYSICIANS**

143 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD),
144 both adult and pediatric, may experience worsening of their depression and/or the emergence of
145 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they
146 are taking antidepressant medications, and this risk may persist until significant remission
147 occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these
148 disorders themselves are the strongest predictors of suicide. There has been a long-standing
149 concern, however, that antidepressants may have a role in inducing worsening of depression and
150 the emergence of suicidality in certain patients during the early phases of treatment. Pooled
151 analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others)
152 showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in
153 children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and
154 other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality
155 with antidepressants compared to placebo in adults beyond age 24; there was a reduction with
156 antidepressants compared to placebo in adults aged 65 and older.

157 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
158 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-
159 term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-
160 controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-
161 term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients.
162 There was considerable variation in risk of suicidality among drugs, but a tendency toward an
163 increase in the younger patients for almost all drugs studied. There were differences in absolute
164 risk of suicidality across the different indications, with the highest incidence in MDD. The risk
165 differences (drug vs placebo), however, were relatively stable within age strata and across

166 indications. These risk differences (drug-placebo difference in the number of cases of suicidality
167 per 1,000 patients treated) are provided in Table 1.

168

169 **Table 1**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

170

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

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

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

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

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

192 **Families and caregivers of patients being treated with antidepressants for major**
193 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**
194 **alerted about the need to monitor patients for the emergence of agitation, irritability,**
195 **unusual changes in behavior, and the other symptoms described above, as well as the**
196 **emergence of suicidality, and to report such symptoms immediately to healthcare**
197 **providers. Such monitoring should include daily observation by families and caregivers.**

198 Prescriptions for PARNATE should be written for the smallest quantity of tablets consistent with
199 good patient management, in order to reduce the risk of overdose.

200 **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial
201 presentation of bipolar disorder. It is generally believed (though not established in controlled
202 trials) that treating such an episode with an antidepressant alone may increase the likelihood of
203 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the
204 symptoms described above represent such a conversion is unknown. However, prior to initiating
205 treatment with an antidepressant, patients with depressive symptoms should be adequately
206 screened to determine if they are at risk for bipolar disorder; such screening should include a
207 detailed psychiatric history, including a family history of suicide, bipolar disorder, and
208 depression. It should be noted that PARNATE is not approved for use in treating bipolar
209 depression.

210 **PARNATE is a potent agent with the capability of producing serious side effects.**

211 PARNATE is not recommended in those depressive reactions where other antidepressant drugs
212 may be effective. **It should be reserved for patients who can be closely supervised and who**
213 **have not responded satisfactorily to the drugs more commonly administered for**
214 **depression.**

215 Before prescribing, the physician should be completely familiar with the full material on
216 dosage, side effects, and contraindications on these pages, with the principles of MAO inhibitor
217 therapy and the side effects of this class of drugs. Also, the physician should be familiar with the
218 symptomatology of mental depressions and alternate methods of treatment to aid in the careful
219 selection of patients for therapy with PARNATE.

220 **Pregnancy Warning:** Use of any drug in pregnancy, during lactation or in women of
221 childbearing age requires that the potential benefits of the drug be weighed against its possible
222 hazards to mother and child.

223 Animal reproductive studies show that PARNATE passes through the placental barrier into
224 the fetus of the rat, and into the milk of the lactating dog. The absence of a harmful action of
225 PARNATE on fertility or on postnatal development by either prenatal treatment or from the milk
226 of treated animals has not been demonstrated. Tranylcypromine is excreted in human milk.

227 **WARNING TO THE PATIENT**

228 Patients should be instructed to report promptly the occurrence of headache or other unusual
229 symptoms, i.e., palpitation and/or tachycardia, a sense of constriction in the throat or chest,
230 sweating, dizziness, neck stiffness, nausea, or vomiting.

231 Patients should be warned against eating the foods listed in Section 11 under
232 Contraindications while on therapy with PARNATE. Also, they should be told not to drink
233 alcoholic beverages. The patient should also be warned about the possibility of hypotension and
234 faintness, as well as drowsiness sufficient to impair performance of potentially hazardous tasks
235 such as driving a car or operating machinery.

236 Patients should also be cautioned not to take concomitant medications, whether prescription or
237 over-the-counter drugs such as cold, hay fever, or weight-reducing preparations, without the
238 advice of a physician. They should be advised not to consume excessive amounts of caffeine in
239 any form. Likewise, they should inform other physicians, and their dentist, about their use of
240 PARNATE.

241 See PRECAUTIONS—Information for Patients for information regarding clinical worsening
242 and suicide risk.

243 **WARNINGS**

244 **Hypertensive Crisis: The most important reaction associated with PARNATE is the**
245 **occurrence of hypertensive crises which have sometimes been fatal.**

246 These crises are characterized by some or all of the following symptoms: occipital headache
247 which may radiate frontally, palpitation, neck stiffness or soreness, nausea or vomiting, sweating
248 (sometimes with fever and sometimes with cold, clammy skin), and photophobia. Either
249 tachycardia or bradycardia may be present, and associated constricting chest pain and dilated
250 pupils may occur. **Intracranial bleeding, sometimes fatal in outcome, has been reported in**
251 **association with the paradoxical increase in blood pressure.**

252 In all patients taking PARNATE, blood pressure should be followed closely to detect
253 evidence of any pressor response. It is emphasized that full reliance should not be placed on
254 blood pressure readings, but that the patient should also be observed frequently.

255 Therapy should be discontinued immediately upon the occurrence of palpitation or frequent
256 headaches during therapy with PARNATE. These signs may be prodromal of a hypertensive
257 crisis.

258 **Important:**

259 **Recommended treatment in hypertensive crises**

260 If a hypertensive crisis occurs, PARNATE should be discontinued and therapy to lower blood
261 pressure should be instituted immediately. Headache tends to abate as blood pressure is lowered.
262 On the basis of present evidence, phentolamine is recommended. (The dosage reported for
263 phentolamine is 5 mg I.V.) Care should be taken to administer this drug slowly in order to avoid
264 producing an excessive hypotensive effect. Fever should be managed by means of external
265 cooling. Other symptomatic and supportive measures may be desirable in particular cases. Do
266 not use parenteral reserpine.

267 **PRECAUTIONS**

268 **Hypotension:** Hypotension has been observed during therapy with PARNATE. Symptoms of
269 postural hypotension are seen most commonly but not exclusively in patients with pre-existent
270 hypertension; blood pressure usually returns rapidly to pretreatment levels upon discontinuation
271 of the drug. At doses above 30 mg daily, postural hypotension is a major side effect and may
272 result in syncope. Dosage increases should be made more gradually in patients showing a
273 tendency toward hypotension at the beginning of therapy. Postural hypotension may be relieved
274 by having the patient lie down until blood pressure returns to normal.

275 Also, when PARNATE is combined with those phenothiazine derivatives or other compounds
276 known to cause hypotension, the possibility of additive hypotensive effects should be considered.

277 There have been reports of drug dependency in patients using doses of tranylcypromine
278 significantly in excess of the therapeutic range. Some of these patients had a history of previous
279 substance abuse. The following withdrawal symptoms have been reported: restlessness, anxiety,
280 depression, confusion, hallucinations, headache, weakness, and diarrhea.

281 Drugs which lower the seizure threshold, including MAO inhibitors, should not be used with
282 Amipaque^{®*}. As with other MAO inhibitors, PARNATE should be discontinued at least 48 hours
283 before myelography and should not be resumed for at least 24 hours postprocedure.

284 MAO inhibitors may have the capacity to suppress anginal pain that would otherwise serve as
285 a warning of myocardial ischemia.

286 The usual precautions should be observed in patients with impaired renal function since there
287 is a possibility of cumulative effects in such patients.

288 Older patients may suffer more morbidity than younger patients during and following an
289 episode of hypertension or malignant hyperthermia. Older patients have less compensatory
290 reserve to cope with any serious adverse reaction. Therefore, PARNATE should be used with
291 caution in the elderly population.

292 Although excretion of PARNATE is rapid, inhibition of MAO may persist up to 10 days
293 following discontinuation.

294 Because the influence of PARNATE on the convulsive threshold is variable in animal
295 experiments, suitable precautions should be taken if epileptic patients are treated.

296 Some MAO inhibitors have contributed to hypoglycemic episodes in diabetic patients
297 receiving insulin or oral hypoglycemic agents. Therefore, PARNATE should be used with
298 caution in diabetics using these drugs.

299 PARNATE may aggravate coexisting symptoms in depression, such as anxiety and agitation.

300 Use PARNATE with caution in hyperthyroid patients because of their increased sensitivity to
301 pressor amines.

302 PARNATE should be administered with caution to patients receiving Antabuse^{®†}. In a single
303 study, rats given high intraperitoneal doses of *d* or *l* isomers of tranylcypromine sulfate plus
304 disulfiram experienced severe toxicity including convulsions and death. Additional studies in rats
305 given high oral doses of racemic tranylcypromine sulfate (PARNATE) and disulfiram produced
306 no adverse interaction.

307 **Information for Patients:** Prescribers or other health professionals should inform patients,
308 their families, and their caregivers about the benefits and risks associated with treatment with
309 PARNATE and should counsel them in its appropriate use. A patient Medication Guide about
310 “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal
311 Thoughts or Actions” is available for PARNATE. The prescriber or health professional should
312 instruct patients, their families, and their caregivers to read the Medication Guide and should
313 assist them in understanding its contents. Patients should be given the opportunity to discuss the
314 contents of the Medication Guide and to obtain answers to any questions they may have. The
315 complete text of the Medication Guide is reprinted at the end of this document.

316 Patients should be advised of the following issues and asked to alert their prescriber if these
317 occur while taking PARNATE.

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

329 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established
330 (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Anyone
331 considering the use of PARNATE in a child or adolescent must balance the potential risks with
332 the clinical need.

333 **ADVERSE REACTIONS**

334 Overstimulation which may include increased anxiety, agitation, and manic symptoms is
335 usually evidence of excessive therapeutic action. Dosage should be reduced, or a phenothiazine
336 tranquilizer should be administered concomitantly.

337 Patients may experience restlessness or insomnia; may notice some weakness, drowsiness,
338 episodes of dizziness or dry mouth; or may report nausea, diarrhea, abdominal pain, or
339 constipation. Most of these effects can be relieved by lowering the dosage or by giving suitable
340 concomitant medication.

341 Tachycardia, significant anorexia, edema, palpitation, blurred vision, chills, and impotence
342 have each been reported.

343 Headaches without blood pressure elevation have occurred.

344 Rare instances of hepatitis, skin rash, and alopecia have been reported.

345 Impaired water excretion compatible with the syndrome of inappropriate secretion of
346 antidiuretic hormone (SIADH) has been reported.

347 Tinnitus, muscle spasm, tremors, myoclonic jerks, numbness, paresthesia, urinary retention,
348 and retarded ejaculation have been reported.

349 Hematologic disorders including anemia, leukopenia, agranulocytosis, and thrombocytopenia
350 have been reported.

351 **Post-Introduction Reports:** The following are spontaneously reported adverse events
352 temporally associated with use of PARNATE. No clear relationship between PARNATE and
353 these events has been established. Localized scleroderma, flare-up of cystic acne, ataxia,
354 confusion, disorientation, memory loss, urinary frequency, urinary incontinence, urticaria,
355 fissuring in corner of mouth, akinesia.

356 **DOSAGE AND ADMINISTRATION**

357 Dosage should be adjusted to the requirements of the individual patient. Improvement should
358 be seen within 48 hours to 3 weeks after starting therapy.

359 The usual effective dosage is 30 mg per day, usually given in divided doses. If there are no
360 signs of improvement after a reasonable period (up to 2 weeks), then the dosage may be
361 increased in 10 mg per day increments at intervals of 1 to 3 weeks; the dosage range may be
362 extended to a maximum of 60 mg per day from the usual 30 mg per day.

363 **OVERDOSAGE**

364 **Symptoms:** The characteristic symptoms that may be caused by overdosage are usually those
365 described above.

366 However, an intensification of these symptoms and sometimes severe additional
367 manifestations may be seen, depending on the degree of overdosage and on individual
368 susceptibility. Some patients exhibit insomnia, restlessness and anxiety, progressing in severe
369 cases to agitation, mental confusion, and incoherence. Hypotension, dizziness, weakness, and
370 drowsiness may occur, progressing in severe cases to extreme dizziness and shock. A few
371 patients have displayed hypertension with severe headache and other symptoms. Rare instances
372 have been reported in which hypertension was accompanied by twitching or myoclonic
373 fibrillation of skeletal muscles with hyperpyrexia, sometimes progressing to generalized rigidity
374 and coma.

375 **Treatment:** Gastric lavage is helpful if performed early. Treatment should normally consist of
376 general supportive measures, close observation of vital signs and steps to counteract specific
377 symptoms as they occur, since MAO inhibition may persist. The management of hypertensive
378 crises is described under WARNINGS in the HYPERTENSIVE CRISES section.

379 External cooling is recommended if hyperpyrexia occurs. Barbiturates have been reported to
380 help relieve myoclonic reactions, but frequency of administration should be controlled carefully
381 because PARNATE may prolong barbiturate activity. When hypotension requires treatment, the
382 standard measures for managing circulatory shock should be initiated. If pressor agents are used,
383 the rate of infusion should be regulated by careful observation of the patient because an
384 exaggerated pressor response sometimes occurs in the presence of MAO inhibition. Remember
385 that the toxic effect of PARNATE may be delayed or prolonged following the last dose of the
386 drug. Therefore, the patient should be closely observed for at least a week. It is not known if
387 tranlycypromine is dialyzable.

388 **HOW SUPPLIED**

389 PARNATE is supplied as round, rose-red, film-coated tablets debossed with the product name
390 PARNATE and SB and contains tranlycypromine sulfate equivalent to 10 mg of
391 tranlycypromine, in bottles of 100 with a desiccant.

392 10 mg 100's: NDC 0007-4471-20

393 Store between 15° and 30°C (59° and 86°F).

394

395 *metrizamide, The Sanofi-Aventis Group.
396 †disulfiram, Odyssey Pharmaceuticals, Inc.

397

398 **Medication Guide**

399 **Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal**

400 **Thoughts or Actions**

401 **PARNATE® (PAR-nate) (tranylcypromine sulfate) Tablets**

402

403 Read the Medication Guide that comes with you or your family member’s antidepressant
404 medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with
405 antidepressant medicines. **Talk to your, or your family member’s, healthcare provider**
406 **about:**

- 407 • All risks and benefits of treatment with antidepressant medicines
- 408 • All treatment choices for depression or other serious mental illness

409

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

412

- 413 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**
414 **teenagers, and young adults within the first few months of treatment.**
- 415 **2. Depression and other serious mental illnesses are the most important causes of suicidal**
416 **thoughts and actions. Some people may have a particularly high risk of having suicidal**
417 **thoughts or actions.** These include people who have (or have a family history of) bipolar
418 illness (also called manic-depressive illness) or suicidal thoughts or actions.
- 419 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**
420 **family member?**
 - 421 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,
422 thoughts, or feelings. This is very important when an antidepressant medicine is started or
423 when the dose is changed.
 - 424 • Call the healthcare provider right away to report new or sudden changes in mood,
425 behavior, thoughts, or feelings.
 - 426 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare
427 provider between visits as needed, especially if you have concerns about symptoms.

428

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

- 431 • Thoughts about suicide or dying
- 432 • Attempts to commit suicide
- 433 • New or worse depression
- 434 • New or worse anxiety

- 435 • Feeling very agitated or restless
- 436 • Panic attacks
- 437 • Trouble sleeping (insomnia)
- 438 • New or worse irritability
- 439 • Acting aggressive, being angry, or violent
- 440 • Acting on dangerous impulses
- 441 • An extreme increase in activity and talking (mania)
- 442 • Other unusual changes in behavior or mood

443

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

- 445 • **Never stop an antidepressant medicine without first talking to a healthcare provider.**
446 Stopping an antidepressant medicine suddenly can cause other symptoms.
- 447 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
448 important to discuss all the risks of treating depression and also the risks of not treating it.
449 Patients and their families or other caregivers should discuss all treatment choices with the
450 healthcare provider, not just the use of antidepressants.
- 451 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the
452 side effects of the medicine prescribed for you or your family member.
- 453 • **Antidepressant medicines can interact with other medicines.** Know all of the medicines
454 that you or your family member takes. Keep a list of all medicines to show the healthcare
455 provider. Do not start new medicines without first checking with your healthcare provider.
- 456 • **Not all antidepressant medicines prescribed for children are FDA approved for use in**
457 **children.** Talk to your child's healthcare provider for more information.

458

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

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462 May 2007

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