PARNATE- tranylcypromine sulfate tablet, film coated
Covis Pharmaceuticals Inc

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 (±)-*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 When tranylcypromine is withdrawn, monoamine oxidase activity is recovered in 3 to 5 days, although the drug is excreted in 24 hours.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.

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

The effectiveness of PARNATE has been established in adult outpatients, most of whom had a depressive illness which would correspond to a diagnosis of Major Depressive Episode Without

Melancholia. As described in the American Psychiatric Association's Diagnostic and Statistical Manual, third edition (DSM III), Major Depressive Episode implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning and includes at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

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

SUMMARY OF CONTRAINDICATIONS

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

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

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

CONTRAINDICATIONS

PARNATE is contraindicated:

1. In patients with cerebrovascular defects or cardiovascular disorders

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

2. In the presence of pheochromocytoma

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

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

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

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

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

Other MAO Inhibitors

Generic Name
Furazolidone
Isocarboxazid

Pargyline HCl
Pargyline HCl and methyclothiazide
Phenelzine sulfate
Procarbazine HCl

Dibenzazepine-Related and Other Tricyclics

Generic Name
Amitriptyline HCl
Perphenazine and amitriptyline HCl
Clomipramine hydrochloride
Desipramine HCl
Imipramine HCl
Nortriptyline HCl
Protriptyline HCl
Doxepin HCl
Carbamazepine
Cyclobenzaprine HCl
Amoxapine
Maprotiline HCl
Trimipramine maleate

4. In combination with bupropion

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

5. In combination with selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs)

As a general rule, PARNATE should not be administered in combination with any SSRI or SNRI. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving a SSRI (e.g., fluoxetine) or a SNRI (e.g., venlafaxine) in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued a SSRI or SNRI and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore SSRIs and SNRIs should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI.

Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping fluoxetine before starting an MAOI.

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

At least one week should be allowed after stopping a SNRI (e.g., venlafaxine) before starting a MAOI.

6. In combination with buspirone

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

7. In combination with sympathomimetics

PARNATE should not be administered in combination with sympathomimetics, including amphetamines which may be found in many herbal preparations as well as over-the-counter drugs such as cold, hay fever or weight-reducing preparations that contain vasoconstrictors.

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

8. In combination with meperidine

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

9. In combination with dextromethorphan

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

10. In combination with cheese or other foods with a high tyramine content

When excessive amounts of tyramine are consumed in conjunction with tranylcypromine, or within 2 weeks of stopping treatment, a serious and sometimes fatal hypertensive reaction may occur.

Tyramine occurs naturally in some foods or may occur from the bacterial breakdown of protein in foods which are fermented, aged, or spoiled. Foods that have reliably been shown to contain a high tyramine content and may also have been reported to induce a serious hypertensive reaction when consumed with tranylcypromine are:

- all matured or aged cheeses (note: all cheeses are considered matured or aged except fresh cottage cheese, cream cheese, ricotta, and processed cheese. All non-cheese dairy products can be consumed providing they are fresh)
- all aged, cured or fermented meat, fish, or poultry (note: meat, fish, or poultry that has not undergone aging, curing or fermenting and that is bought fresh, stored correctly and eaten fresh is not contraindicated)
- all fermented soybean products (e.g., soy sauce, miso, fermented tofu)
- sauerkraut
- fava or broad bean pods
- banana peel (but not the pulp)
- concentrated yeast extracts (e.g., Marmite or Vegemite spread)
- all tap/draught beers (note: some bottled beers, including non-alcoholic beer, may also pose a risk).

Patients should be advised to minimize or avoid use of all alcoholic beverages while taking PARNATE. Patients should be advised to adhere to the following dietary guidance about eating fresh foods:

Foods may be deliberately aged as part of their processing and these are contraindicated (*see list above*).

Foods may also naturally age over time, even if they are refrigerated. It is therefore extremely important that patients are instructed to buy and eat only fresh foods or those which have been properly frozen. They should avoid eating foods if they are unsure of their storage conditions or freshness and they should be cautious of foods of unknown age or composition even if refrigerated.

The longer food is left to deteriorate and the larger the quantity of food eaten, the greater the potential quantity of tyramine ingested. Where there is any doubt, patients should be advised to either avoid the food or consume it in strict moderation if it is not otherwise contraindicated.

Patients should also be warned that tyramine levels may vary by brand or even batch and a person may absorb different amounts of tyramine from a particular food at different times. Therefore, if they have accidentally consumed a prohibited food on one occasion and not had a reaction, this does not mean that they will not have a serious hypertensive reaction if they consume the same food on a different occasion.

11. In patients undergoing elective surgery

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

ADDITIONAL CONTRAINDICATIONS

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

1. PARNATE should not be used in combination with some central nervous system depressants such as narcotics and alcohol, or with hypotensive agents. A marked potentiating effect on these classes of drugs has been reported.

2. Anti-parkinsonism drugs should be used with caution in patients receiving PARNATE since severe reactions have been reported.

3. PARNATE should not be used in patients with a history of liver disease or in those with abnormal liver function tests.

4. Excessive use of caffeine in any form should be avoided in patients receiving PARNATE.

WARNINGS TO PHYSICIANS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. 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 with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive

compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

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

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

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

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

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

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

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for PARNATE should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

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

PARNATE is a potent agent with the capability of producing serious side effects. PARNATE is not recommended in those depressive reactions where other antidepressant drugs may be effective. **It should be reserved for patients who can be closely supervised and who have not responded satisfactorily to the drugs more commonly administered for depression.**

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

Pregnancy Warning

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

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

WARNING TO THE PATIENT

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

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

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

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

WARNINGS

Hypertensive Crisis

The most important reaction associated with PARNATE is the occurrence of hypertensive crises which have sometimes been fatal.

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

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

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

Important:

Recommended treatment in hypertensive crises

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

PRECAUTIONS

Hypotension

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

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

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

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

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

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

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

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

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

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

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

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

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

Information for Patients

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

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

Clinical Worsening and Suicide Risk

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

Pediatric Use

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

ADVERSE REACTIONS

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

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

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

Headaches without blood pressure elevation have occurred.

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

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

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

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

Post-Introduction Reports

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

DOSAGE AND ADMINISTRATION

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

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

OVERDOSAGE

Symptoms

The characteristic symptoms that may be caused by overdosage are usually those described above.

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

Treatment

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. Telephone numbers for the certified Poison Control Centers are listed in the *Physicians' Desk Reference* (PDR).

Treatment should normally consist of general supportive measures, close observation of vital signs and steps to counteract specific symptoms as they occur, since MAO inhibition may persist. The management of hypertensive crises is described under WARNINGS in the HYPERTENSIVE CRISES section.

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

HOW SUPPLIED

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

10 mg 100's: NDC 24987-447-10

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

*Amipaque, Nycomed Inc.

†Antabuse, TEVA Women's Health, Inc.

Medication Guide

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

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

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

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

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

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.

- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

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

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Trouble sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking (mania)
- Other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

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

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COVIS

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Cary, NC 27511

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Mississauga, ON, Canada L5N 6L4

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PRINCIPAL DISPLAY PANEL

Bottle Label

NDC 24987-447-10100 Tablets

Parnate®
(tranylcypromine sulfate)
Tablets

10 mg

Federal Law requires dispensing of PARNATE® with the Medication Guide under this label.

R_x only

COVIS

Store tablets between 15º and 30ºC (59º and 86ºF). Dispense in a tight, light-resistant container. Each tablet contains tranylcypromine, 10 mg, as the sulfate.

Usual Dosage: 30 mg per day, usually given in divided doses. See accompanying prescribing information.

Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Dist. by Covis Pharmaceuticals, Inc.
Cary, NC 27511
Mfd. by GlaxoSmithKline
Mississauga, ON, Canada L5N 6L4

Made in Italy 100025 Rev. 5/12

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PARNATE
tranylcypromine sulfate tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:24987-447
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TRANYLCYPROMINE SULFATE (UNII: 7ZAT6ES870) (TRANYLCYPROMINE - UNII:3E3V44J4Z9)	TRANYLCYPROMINE	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
D&C RED NO. 7 (UNII: ECW0LZ41X8)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
GELATIN (UNII: 2G86QN327L)	
LACTOSE (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	RED (rose-red)	**Score**	no score
Shape	ROUND	**Size**	4mm
Flavor		**Imprint Code**	PARNATE;SB
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:24987-447-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/14/2013	09/30/2017

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA012342	01/14/2013	09/30/2017

Labeler - Covis Pharmaceuticals Inc (969968986)