PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrPARNATE

tranylcypromine tablets USP

10 mg tranylcypromine (as tranylcypromine sulfate)

Antidepressant

GlaxoSmithKline Inc.
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Mississauga, Ontario
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PARNATE (tranylcypromine sulfate) is indicated for the treatment of major depressive disorder (MDD) in adult patients who have not responded adequately to other antidepressants. PARNATE is not indicated for the initial treatment of MDD due to the potential for serious adverse reactions and drug interactions, and the need for dietary restrictions.

Pediatrics

Pediatrics (<18 years of age): PARNATE is not indicated for use in children or adolescents less than 18 years of age.

Geriatrics

Geriatrics: No data are available.

2 CONTRAINDICATIONS

PARNATE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

PARNATE is contraindicated in patients with the following (see **WARNINGS AND PRECAUTIONS**):

- Cerebrovascular or cardiovascular disorders (e.g., arteriosclerosis, hypertension).
- History of recurrent or frequent headaches.
- Liver damage or blood dyscrasias.
- Phaeochromocytoma and catecholamine-releasing paragangliomas.

PARNATE is contraindicated in combination with the following medications (before, during or shortly after). (see **DRUG INTERACTIONS**):

- Other monoamine oxidase inhibitors (MAOIs) (e.g. phenelzine sulphate, isocarboxazid, nialamide, pargyline)
- Selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g. venlafaxine)
- Tricyclic antidepressants (dibenzazepine derivatives, e.g. amitriptyline, nortriptyline, protriptyline, desipramine, imipramine, doxepin, perphenazine, carbamazepine, cyclobenzaprine, amoxapine, maprotiline, trimipramine, and clomipramine hydrochloride)
- Other antidepressant drugs (e.g. amoxapine, bupropion, maprotiline, nefazodone, trazodone, vilazodone, vortioxetine)

- Serotonin releasing agents (e.g. amphetamine and methylphenidate and their derivatives)
- Triptans (e.g. sumatriptan or rizatriptan)
- Sympathomimetics (e.g. pseudoephedrine, phenylephedine, ephedrine, methyldopa, dopamine, and levodopa and tryptophan), including those contained in cold, hay fever or weight-reducing products, herbal products, and diet supplements
- Other individual drugs in the following list buspirone, carbamazepine, cyclobenzaprine, dextromethorphan, dopamine, hydroxytryptophan, levodopa, meperidine, methyldopa, milnacipran, rasagiline, reserpine, s-adenosyl-L-methionine (SAM-e), tapentadol, tetrabenazine, tryptophan
- Foods and beverages with a high tyramine content

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Suicidal Thoughts and Behaviors** Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors (see **WARNINGS AND PRECAUTIONS**). PARNATE is not approved for use in pediatric patient.

- **Hypertensive crisis:** When excessive amounts of tyramine are consumed in conjunction with PARNATE, or within 2 weeks of stopping treatment, a serious and sometimes fatal hypertensive reaction may occur (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Hypertensive crisis**).

4.1 Dosing Considerations

Dosage should be adjusted to the requirements of the individual patient. If the patient responds to therapy, the response is usually seen within 48 hours to 3 weeks after starting medication.

4.2 Recommended Dose and Dosage Adjustment

Recommended starting dosage is 20 mg per day (10 mg in the morning and 10 mg in the afternoon).

If no signs of a response appear within 2 to 3 weeks, increase dosage to 30 mg daily (20 mg in the morning and 10 mg in the afternoon). Continue this dosage for at least 1 week. If no improvement occurs, continued administration is unlikely to be beneficial. Although dosages above 30 mg per day have been used, consider that the incidence and severity of side effects may increase as dosage is raised.

Dosage increases should be made in increments of 10 mg per day at intervals of 1 to 3 weeks to a maximum daily dose of 60 mg.

When a satisfactory response is obtained, dosage may be reduced to a maintenance level.

Some patients will be maintained on 20 mg per day; many will need only 10 mg daily.

When Electroconvulsive therapy (ECT) is being administered concurrently with PARNATE, 10 mg BID can usually be given during the series, then reduced to 10 mg daily for maintenance therapy.

Switching to or from other Contraindicated Drugs
Allow 1 week to elapse between the discontinuance of PARNATE and the administration of any other drug that is contraindicated with PARNATE. The prescribing information for individual products should be consulted.

Because the effect of many antidepressant drugs may persist for 10 to 20 days, do not start PARNATE treatment within less than 1 week of discontinuing treatment with such drugs; then use half the normal dosage for the first week.

Discontinuing Treatment
Consider discontinuing PARNATE therapy by slow, gradual dosage reduction.

Withdrawal effects, including delirium, have been reported with abrupt discontinuation of PARNATE therapy. Higher daily doses and longer duration of use appear to be associated with a higher risk of withdrawal effects.

When tranylcypromine is withdrawn, monoamine oxidase activity is recovered in 3 to 5 days, although the drug is excreted in 24 hours; however, inhibition of MAO activity may persist for up to 1 week.

Geriatrics (>60 years of age): Use with caution. Consider more gradual dosage increases as this population may have an increased risk for hypotension (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Pediatrics (<18 years of age): PARNATE is not indicated for use in children or adolescents less than 18 years of age.

4.3 Administration

Instruct patients to:

- avoid foods and beverages with high tyramine content while being treated with PARNATE and for 2 weeks after stopping PARNATE (see **CONTRAINDICATIONS**)
- avoid use of all alcoholic beverages while taking PARNATE
- take their dose of PARNATE at approximately the same time each day. Taking the last dose before 3 p.m. may be a potential method for managing insomnia.

4.4 Missed Dose

In the case of a missed dose of PARNATE, instruct patients to take their next dose at its regularly scheduled time.

5 OVERDOSAGE

Symptoms
The characteristic symptoms are usually those which have already been described under **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**; 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
Treatment normally consists of general supportive measures, close observation of vital signs and steps to counteract specific symptoms as they occur.
The management of hypertensive crisis is described in **WARNINGS AND PRECAUTIONS, Cardiovascular, Hypertensive Crisis**.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet /10 mg tranylcypromine (as tranylcypromine sulfate)	Carnauba Wax, Citric Acid, Croscarmellose Sodium, D&C red No. 7, FD&C Blue No. 2, FD&C yellow No. 6 aluminium lake (Sunset Yellow), Gelatin, Hydroxypropyl methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Purified Water, Talc, Titanium Dioxide

PARNATE tablets are biconvex, rose-red, round, film-coated tablets, debossed with “PARNATE” and “SB” on one side.

Available in bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

Please see the **SERIOUS WARNINGS AND PRECAUTIONS BOX** at the beginning of Part I: Health Professional Information.

Cardiovascular

Hypertensive crisis: The most important adverse reaction associated with PARNATE is hypertensive crisis, which has sometimes been fatal. This response is not usually dose-related. It is associated with a distinctive reaction 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) with early pallor followed later by flushing, and photophobia. Either tachycardia or bradycardia may be present, sometimes associated with constricting chest pain. Mydriasis may occur.

The occipital headache, together with pain and stiffness in the cervical muscles, may mimic subarachnoid hemorrhage, but can equally be associated with actual intracranial bleeding, as in other conditions where a sudden rise in blood pressure occurs. Cases of such bleeding have been reported, some of which have been fatal.

Blood pressure should be followed closely in patients taking PARNATE 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.

If a hypertensive reaction occurs, PARNATE should be discontinued. Patients should be managed according to standard of care.

Hypotension: Hypotension, which may be postural, has been observed during PARNATE therapy, particularly at doses above 30 mg daily. It is seen most commonly (but not exclusively) in patients with pre-existing hypertension. In most instances, it affects the systolic readings. Rare instances of syncope have been seen. Dosage increases should be made more gradually in patients showing a tendency toward hypotension at the starting dose. Postural hypotension can usually be relieved by having the patient lie down until blood pressure returns to normal. This side effect is usually temporary, but if it persists, PARNATE should be discontinued. Blood pressure usually returns rapidly to pre-treatment levels upon discontinuation of PARNATE.

When PARNATE is combined with phenothiazine derivatives (e.g. triluoperazine) or other compounds known to cause hypotension, the possibility of additive hypotensive effects should be considered (see **DRUG INTERACTIONS**).

Angina: MAOIs may have the capacity to suppress anginal pain that would otherwise serve as a warning of myocardial ischemia.

Dependence/Tolerance
There have been reports of drug dependency in patients using doses of PARNATE significantly in excess of the therapeutic range. Some of these patients had a history of previous substance abuse.

PARNATE should be tapered according to the patient's clinical reaction when discontinuation is necessary. Symptoms reported after stopping PARNATE without tapering include sleep disturbances, depression, confusion, delirium, tremor, agitation, convulsion, anxiety, hallucinations, fatigue, and headache.

Driving and Operating Machinery
Some PARNATE adverse reactions (e.g. dizziness, drowsiness, etc.) may affect the patient's ability to drive or operate machinery. For patients who experience these symptoms, due caution should be exercised when driving or operating a vehicle or potentially dangerous

machinery.

Endocrine and Metabolism
Hyperthyroidism: Use PARNATE with caution in hyperthyroid patients because of their increased sensitivity to pressor amines.

Hematologic
Diabetes: Some MAOIs have contributed to hypoglycemic episodes in diabetic patients receiving insulin or oral hypoglycemic agents. Therefore, PARNATE should be used with caution in diabetics under treatment with these drugs.

Hepatic/Biliary/Pancreatic
Patients with liver damage or blood dyscrasias: Extensive clinical use and laboratory tests have revealed no evidence of liver toxicity or blood dyscrasias due to PARNATE therapy. Because rare cases of hepatitis have been reported, it is recommended that patients with known liver damage or blood dyscrasias should not be treated with PARNATE.

Immune
Hypersensitivity: The tablet coating contains an azo dye (FD&C Yellow No. 6 aluminium lake) which may cause allergic reactions.

Monitoring and Laboratory Tests
Cardiovascular Monitoring**:** Blood pressure should be followed closely in patients taking PARNATE 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.

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

Ophthalmologic
Angle-closure Glaucoma: As with other antidepressants, PARNATE can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Patients should be examined to determine whether they are susceptible to angle-closure and be informed to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Peri-Operative Considerations
Discontinue PARNATE at least 7 days before elective surgery because of possible interference with the action of certain anesthetics and analgesics.

As with other MAOIs, PARNATE should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours after the procedure.

Psychiatric
Potential Association with the Occurrence of Behavioral and Emotional Changes, Including Self-Harm: It is unknown whether increased risk of suicidal ideation and behavior is associated with the use of PARNATE in pediatric patients and/ or adults.

However, recent analyses of placebo-controlled clinical trial safety databases from SSRIs and

other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioral and emotional changes, including an increased risk of suicidal ideation and behavior over that of placebo. Thus, rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behavior is advised in patients of all ages given any antidepressant drug. This includes monitoring for emotional and behavioral changes.

Clinical worsening and suicide risk in adults with psychiatric disorders: Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicidal behaviour or thoughts, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and / or the emergence of suicidal ideation / behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognized that the onset of some neuropsychiatric symptoms could be related either to the underlying disease state or the drug therapy (see **Mania and bipolar disorder** below).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and / or the emergence of suicidal ideation / behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Depression*:* PARNATE may aggravate coexisting symptoms in depression, such as anxiety and agitation. In depressed patients, the possibility of suicide should always be considered, and adequate precautions taken. Exclusive reliance on drug therapy to prevent suicidal attempts is unwarranted, as there may be a delay in the onset of therapeutic effect or an increase in anxiety and agitation. Also, some patients fail to respond to drug therapy or may respond only temporarily.

Mania and 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 can increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients 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. As with all antidepressants, tranylcypromine should be used with caution in patients with a history of mania.

Insomnia: It is the most frequent adverse reaction to PARNATE, which can usually be

overcome by giving the last dose of the day no later than 3 p.m., by reducing the dose, or other measures of standard of care.

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

7.1 Special Populations

7.1.1 Pregnant Women

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available. PARNATE has been shown to pass through the placental barrier to the fetus of the rat. PARNATE is not recommended for a pregnant patient.

7.1.2 Breast-feeding

Adequate human data on use during lactation are not available. PARNATE has been shown to pass into the human milk. PARNATE is not recommended for a breast-feeding patient.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available. PARNATE is not indicated for use in children or adolescents less than 18 years of age.

7.1.4 Geriatrics

Geriatrics (>60 years of age): Caution is advised in this population because of higher risks of cardiovascular abnormalities. (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

8 ADVERSE REACTIONS

The most serious adverse reactions are as follows:
- Hypertensive crisis (see **SERIOUS WARNINGS AND PRECAUTIONS BOX**)
- New or Worsened Emotional or Behavioral Problems (see **SERIOUS WARNINGS AND PRECAUTIONS BOX**)
- Hypotension (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension**)

The following adverse reactions have been identified in clinical trials or during post-approval use of PARNATE.

Blood and lymphatic system disorders: agranulocytosis, leukopenia, thrombocytopenia, anemia
Metabolism and nutrition disorders: anorexia

Psychiatric disorders: overstimulation, manic symptoms, agitation, insomnia, anxiety, confusion, depression, delirium, hallucinations, habituation

Nervous system disorders: dizziness, restlessness, tremor, muscle spasm, paresthesia, drowsiness, headaches (without blood pressure elevation), convulsion

Eye disorders: blurred vision

Ear and labyrinth disorders: tinnitus

Cardiac disorders: tachycardia, palpitations

Vascular disorders: hypertensive crisis, hypotension

Gastrointestinal disorders: diarrhea, constipation, nausea, abdominal pain, dry mouth

Hepatobiliary disorders: hepatitis

Skin and subcutaneous tissue disorders: rash, alopecia, sweating

Renal and urinary disorders: urinary retention, micturition

Reproductive system and breast disorders: impotence

General disorders and administration site conditions: edema, chills, weakness, fatigue, sleep disturbances

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Serious Drug Interactions

Foods and Beverages with a High Tyramine Content: When excessive amounts of tyramine are consumed in conjunction with PARNATE, or within 2 weeks of stopping treatment, a serious and sometimes fatal hypertensive reaction may occur (see **CONTRAINDICATIONS**)

9.2 Overview

In general, the physician should bear in mind the possibility of a lowered margin of safety when PARNATE (tranylcypromine sulfate) is administered in combination with potent drugs and should adjust dosage accordingly.

9.3 Drug-Drug Interactions

The drugs listed in this Table 2 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Drug Class and/or Product	Clinical comment	Effect
Other monoamine oxidase inhibitors (MAOIs) (e.g. phenelzine sulphate, isocarboxazid, nialamide, pargyline).	Contraindicated	Increased MAO inhibition and risk of adverse reactions, serotonin syndrome and hypertensive reaction
Selective serotonin reuptake inhibitors (SSRIs) **Serotonin and noradrenaline reuptake inhibitors (SNRIs)** (e.g. venlafaxine) **Serotonin releasing agents** (e.g. amphetamine and derivatives). Other antidepressants, such as tricyclics, tetracyclics, etc.	Contraindicated	Serotonin Syndrome
Dibenzazepine derivatives (e.g. amitriptyline, nortriptyline, protriptyline, desipramine, imipramine, doxepin, perphenazine, carbamazepine, cyclobenzaprine, amoxapine, maprotiline, trimipramine, and clomipramine hydrochloride).	Contraindicated	Hypertensive crises or severe convulsive seizures Clomipramine hydrochloride, when used in combination with a MAOI, has been reported to result in hyperpyrexia, diffuse intravascular coagulation, and status epilepticus.
Triptans (e.g. sumatriptan or rizatriptan).	Contraindicated	Serotonin Syndrome

Sympathomimetics – (e.g. amphetamines, ephedrine, methyldopa, dopamine, and levodopa and tryptophan). Other products that may contain sympathomimetics: Medication without prescription for cold or hay fever (including nose drops or sprays); Herbal products or supplements; energy-enhancing or weight-reducing products; recreational drugs such as 3,4-Methy-lenedioxy-methamphetamine (MDMA, ecstasy)	Contraindicated	These may result in potentiation, precipitating hypertension, severe headache, and hyperpyrexia. Cerebral (subarachnoid) hemorrhage may also occur. The combination of MAOIs and tryptophan has been reported to cause behaviour and neurologic syndromes including disorientation, confusion, amnesia, delirium, agitation, hypomanic signs, ataxia, myoclonus, hyperreflexia, shivering, ocular oscillations and Babinski signs.
Dextromethorphan	Contraindicated	Serotonin Syndrome
buspirone HCl	Contraindicated	Hypertensive Reaction
Central Nervous System (CNS) depressants (e.g. morphine, opioids, meperidine, barbiturates)	Use with caution	Increased CNS depression
Hypotensive agents (e.g. guanethidine, reserpine, alpha-methyldopa)	Use with caution	Additive hypotensive effects
Antidiabetic Drugs - Insulin or oral hypoglycemic agents	Use not recommended unless benefits out weight risks	Some MAOIs have contributed to hypoglycemic episodes
Phenothiazine drugs (e.g. trifluoperazine, chlorpromazine)	Use not recommended unless benefits out weight risks	Risks of hypotension and hypertensive crisis.
Treatments for Parkinson's disease Note: Levodopa, as a sympathomimetic, is contraindicated to be combined with PARNATE.	Use not recommended unless benefits out weight risks	Combination may result in potentiation, with profuse sweating, tremulousness, and a rise in body temperature
disulfiram	Use with caution	Combination may result in severe toxicity.

9.4 Drug-Food Interactions

PARNATE inhibits intestinal MAO, which is responsible for the catabolism of tyramine in food and beverages. As a result of this inhibition, large amounts of tyramine may enter the systemic circulation and precipitate a sudden elevation in blood pressure or hypertensive crisis (see **WARNINGS AND PRECAUTIONS**). Instruct PARNATE-treated patients to avoid foods and beverages with significant tyramine content during treatment with PARNATE or within 2 weeks of stopping treatment (see Table 3 for a list of food and beverages containing significant amounts of tyramine).

Table 3 - Foods and Beverages with and without Significant Amounts of Tyramine

Class of Food or Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods and Drinks, Containing No or Little Tyramine
Meat, Poultry, and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry, and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry, and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese, and yogurt
Beverages	All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation and excessive amounts of caffeine.	Concomitant use of alcohol with PARNATE is not recommended. (Bottled and canned beers and wines contain little or no tyramine.)
Other	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu), OTC supplements containing tyramine, and chocolate	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

Foods may be deliberately aged as part of their processing and should be avoided (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 in strict moderation.

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.

PARNATE may potentiate the effects of alcoholic beverages.

9.5 Drug-Herb Interactions

Caution should be exercised when giving PARNATE with St. John's wort, as the development of serotonin toxicity has been reported with MAOIs when given before, with, or shortly after discontinuation of this drug. Observation of tranylcypromine washout period of at least 1 week is recommended.

9.6 Drug-Laboratory Test Interactions

Drugs which lower the seizure threshold, including MAO inhibitors, should not be used with metrizamide.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of action of PARNATE as an antidepressant is not fully understood but is presumed to be linked to potentiation of monoamine neurotransmitter activity in the central nervous system (CNS) resulting from its irreversible inhibition of the enzyme monoamine oxidase (MAO).

10.2 Pharmacodynamics

When tranylcypromine is withdrawn, monoamine oxidase activity is gradually restored within a week, although the drug is excreted in 24 hours.

10.3 Pharmacokinetics

Absorption: Tranylcypromine is rapidly absorbed from the gastrointestinal tract following oral administration. Peak plasma concentrations occur within 1 hour of dosing.

Distribution: Tranylcypromine is distributed widely throughout the body.

Metabolism: No text available.

Elimination: The drug is excreted in the urine, mainly in the form of metabolites.

11 STORAGE, STABILITY AND DISPOSAL

PARNATE tablet should be stored at 15-30°C. Keep out of the sight and reach of children.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: tranylcypromine sulfate

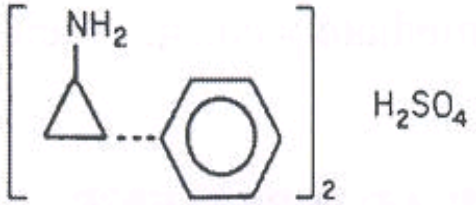
Chemical name: (±)-trans-2-phenylcyclopropylamine sulfate (2:1)

Molecular formula: $(C_9H_{11}N)2.H_2SO_4$

Molecular Mass: 133.19 (free base)

364.47 (sulfate salt)

Structural formula:



Physicochemical properties: A white or almost white, crystalline powder; odourless or with a faint odour similar to that of cinnamaldehyde. It is soluble in water, very slightly soluble in ethanol (96%) and in ether, insoluble in chloroform.

13 CLINICAL TRIALS

Not Available.

14 NON-CLINICAL TOXICOLOGY

No further information of clinical relevance.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]PARNATE
tranylcypromine tablets USP

Read this carefully before you start taking PARNATE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about PARNATE.

Serious Warnings and Precautions

- **Suicidal Thoughts and Behaviors**: In studies, antidepressants were shown to increase the risk of suicidal thoughts and behaviors in young adults and patients under 18 years of age. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your healthcare professional immediately. You will need to be closely monitored by a healthcare professional during treatment with PARNATE.

- **Dangerous Increase in Blood Pressure:** Certain foods and drinks must be avoided during treatment with PARNATE and for 2 weeks after stopping treatment. If you do not avoid certain foods and drinks, you may have a dangerous increase in blood pressure that can lead to death. A complete list of those foods and drinks are included in the section called “Foods and Beverages to avoid while taking PARNATE”.

What is PARNATE used for?
PARNATE is used for the treatment of major depressive disorder (MDD). It is only for use in adults who have not responded well to other antidepressants. PARNATE is not for the initial treatment of MDD.

How does PARNATE work?
PARNATE belongs to the family of medicines called monoamine oxidase inhibitors (MAOIs). PARNATE helps with the symptoms of depression.

What are the ingredients in PARNATE?
Medicinal ingredients: tranylcypromine (as tranylcypromine sulfate)

Non-medicinal ingredients: carnauba wax, citric acid, croscarmellose sodium, D&C red No. 7, FD&C Blue No. 2, FD&C yellow No. 6 aluminium lake (Sunset Yellow), gelatin, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, purified water, talc and titanium dioxide.

PARNATE comes in the following dosage forms:
Tablet, 10mg tranylcypromine (as tranylcypromine sulfate)

Do not use PARNATE if you:

- are allergic to the active ingredient, tranylcypromine or any of the components of its formulation or packaging
- have high blood pressure or heart disease
- have ever had a stroke, or any other kind of disorder related to the brain and its blood vessels
- have liver disease
- have a blood disorder
- have a history of severe or frequent headaches
- have a tumor of the adrenal gland (pheochromocytoma) or a type of tumor called a paraganglioma
- were recently or are taking any other medicine for depression or anxiety
- were or are taking any of the following:
    - carbamazepine, used to treat seizures
    - cyclobenzaprine, used as a muscle relaxant
    - sumatriptan, rizatriptan and other triptans, used to treat migraines and cluster headaches
    - non-prescription medications to treat colds or hay fever, including drops or sprays
    - natural health products that are for increased energy or weight loss
    - street drugs including MDMA and ecstasy
    - amphetamines, used to treat attention deficit disorder
    - products containing ephedrine, used to treat nasal congestion
    - methyldopa, used to treat high blood pressure
    - dopamine, used in hospital to treat certain medical emergencies
    - levodopa, used to treat Parkinson's disease
    - dextromethorphan, used as a cough suppressant

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PARNATE. Talk about any health conditions or problems you may have, including if you:

- have a history of kidney or heart problems
- have diabetes
- have epilepsy
- have an overactive thyroid gland
- have mania or bipolar disorder
- have or have ever had recurrent or frequent headaches
- are pregnant, plan to become pregnant, or are breastfeeding
- are beyond the age of sixty
- drink alcohol and /or use street drugs
- recently had a surgery or are planning to have surgery
- are allergic to a yellow dye called FD&C Yellow No. 6 aluminium lake.

Other warnings you should know about:

In the first few weeks of taking PARNATE or when your dose changes, you may feel worse instead of better. You may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your healthcare professional immediately.

PARNATE may cause an acute attack of glaucoma. Having your eyes examined before you take this drug could help identify if you are at risk of having angle-closure glaucoma.

PARNATE may affect your ability to drive or operate machinery. Wait until you know how you feel after taking PARNATE before driving or using heavy machines.

PARNATE may cause insomnia. To help you sleep better, take your afternoon dose no later than 3pm.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PARNATE. Your healthcare professional will help you know if it is safe for you to take PARNATE with the drugs listed below**:**

- opioids, morphine, meperidine, used for treatment of pain
- barbiturates, used as sedatives
- guanethidine, reserpine, alpha-methyldopa, used to treat high blood pressure
- insulin or other oral drugs to treat low blood sugar
- trifluoperazine, used to treat schizophrenia and anxiety
- chlorpromazine, used to treat schizophrenia and depression
- disulfiram, used to treat chronic alcoholism
- treatments for Parkinson's disease
- St. John's Wort, a natural health product used to treat depression

Foods and Beverages to avoid while taking PARNATE:
A process of aging or breakdown is used to improve the flavor certain foods. It is important to avoid foods that contain high amounts of tyramine while you are taking PARNATE. Tyramine can interact with PARNATE to cause dangerously high blood pressure. It is very important that you buy and eat only fresh foods or those that have been properly frozen. Fresh foods can age naturally over time, so make sure to eat them when they are fresh.

The table below lists foods to avoid while taking PARNATE and for 2 weeks after stopping it. There are also suggestions of acceptable foods and drinks to help guide you.

Class of Food or Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods and Drinks, Containing No or Little Tyramine
Meat, Poultry, and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry, and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry, and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta

		cheese, cottage cheese, and yogurt
Beverages	All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation and excessive amounts of caffeine.	Use of alcohol with PARNATE is not recommended. (Bottled and canned beers and wines contain little or no tyramine.)
Other	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu), non-prescription drugs and natural health products containing tyramine, and chocolate	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

Check the ingredients of foods or drinks that you have not prepared yourself, including pre-prepared foods and restaurant foods. Speak with your healthcare professional if you have any questions.

How to take PARNATE:

- Take the tablets in the morning and again mid-afternoon. It is better if you take your tablets at the same time every day.
- You should continue to take your medicine even if you do not feel better, as it may take a few weeks for your medicine to work.
- It is important that you take PARNATE exactly as your healthcare professional has instructed. Do not stop taking your medication on your own.
- When it is time to stop taking PARNATE, your healthcare professional will guide you about how to stop taking it slowly to help avoid side effects.

Usual dose:
The usual starting dose of PARNATE is one 10 mg tablet taken 2 times a day (morning and afternoon).

Remember: This medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.

Overdose:

If you think you have taken too much PARNATE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using PARNATE?
These are not all the possible side effects, you may feel when taking PARNATE. If you experience any side effects not listed here, contact your healthcare professional.

Possible side effects of PARNATE include the following:

- trouble sleeping

- feeling sick (nausea)
- dry mouth
- feeling tired or sleepy
- weakness
- dizziness
- loss of appetite
- diarrhea
- constipation
- headache
- muscle spasms, twitches or shakiness
- restlessness
- tingling or prickling feeling
- ringing or buzzing in the ears
- abdominal pain
- swelling
- chills

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic reactions including but not limited to red and lumpy skin rash, hives, swelling in the mouth, tongue, face and throat, itching, rash, trouble breathing		✓	
VERY RARE			
Unusual hair loss or thinning		✓	
UNKNOWN			
New or Worsened Emotional or Behavioral Problems: unusual feelings of agitation, hostility or anxiety, impulsive or disturbing thoughts such as thoughts of self-harm or harm to others		✓	
Dangerous Increase in Blood Pressure (Hypertensive crisis): severe or frequent headaches, chest pain, fast or slow heartbeat, neck stiffness or soreness, sweating with initial paleness followed by flushing of the skin, enlarged pupils, nausea, vomiting and unusual bleeding or bruising			✓
Drug Dependence and Discontinuation Symptoms: withdrawal symptoms may include sleep disturbances, depression, confusion, delirium, tremor, agitation, convulsion, anxiety, nervousness, hallucinations, headache		✓	
Glaucoma: blurred vision, eye pain, changes in vision, swelling or redness in or around the eye		✓	
Urinary retention: difficulty passing urine		✓	

Low Blood Pressure: severe dizziness or fainting on standing		✓	
Overstimulation: symptoms may include feeling excessive happiness or irritability, agitation, anxiety, greatly increased energy, racing thoughts, talking more or faster than usual, reckless behavior		✓	
Low red blood cells (Anemia): being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, or weakness		✓	
Low white blood cells - neutrophils and leukocytes (Agranulocytosis and Leukopenia): fever or infection, fatigue, aches and pains, and flu-like symptoms		✓	
Low blood platelets (Thrombocytopenia): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	
Inflammation of the liver (Hepatitis): yellow discoloration of the skin and whites of the eyes, dark urine, vomiting, and abdominal pain		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15 and 30°C. Keep out of the sight and reach of children.

If you want more information about PARNATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.gsk.ca or by calling 1-800-387-7374

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