

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use TRANLYCYPROMINE SULFATE TABLETS safely and effectively. See full prescribing information for TRANLYCYPROMINE SULFATE TABLETS.

TRANLYCYPROMINE SULFATE tablets, for oral use

Initial U.S. Approval: 1961

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS AND HYPERTENSIVE CRISIS WITH SIGNIFICANT TYRAMINE USE

See full prescribing information for complete boxed warning.

- Increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Tranlycypromine Sulfate is not approved for use in pediatric patients. (5.1, 8.4)
- Excessive consumption of foods or beverages with significant tyramine content or certain drugs can precipitate hypertensive crisis. Monitor blood pressure, allow for medication free intervals, and advise patients to avoid foods and beverages with high tyramine content. (5.2, 7.1, 7.2)

- INDICATIONS AND USAGE
- Tranlycypromine Sulfate is a monoamine oxidase inhibitor (MAOI) indicated for the treatment of major depressive disorder (MDD) in adult patients who have not responded adequately to other antidepressants (1)
 - Tranlycypromine Sulfate 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 (1, 4, 5, 7)

- DOSAGE AND ADMINISTRATION
- Recommended daily dosage is 30 mg in divided doses (2.1)
 - If no adequate response, increase dosage in increments of 10 mg per day every 1 to 3 weeks to a maximum dosage of 30 mg twice daily (60 mg per day). Consider more gradual dosage increases in patients at risk for hypotension (2.1)
 - Consider discontinuing tranlycypromine sulfate therapy gradually because of the risk for withdrawal effects (2.3, 5.8, 9.3)

- FULL PRESCRIBING INFORMATION: CONTENTS*
- WARNING: SUICIDAL THOUGHTS AND BEHAVIORS and HYPERTENSIVE CRISIS WITH SIGNIFICANT TYRAMINE USE**

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

2.2 Switching to or from Other Antidepressants

2.3 Discontinuing Treatment

2.4 Screen for Bipolar Disorder and Elevated Blood Pressure Prior to Starting Tranlycypromine Sulfate

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

4.1 Combination with Certain Drugs

4.2 Pheochromocytoma, Catecholamine-Releasing Paragangliomas

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

5.2 Hypertensive Crisis and Hypertension

5.3 Serotonin Syndrome

5.4 Activation of Mania/Hypomania

5.5 Hypotension

5.6 Hypotension and Hypertension during Anesthesia and Perioperative Care

5.7 Need for Emergency Treatment with Contraindicated Drugs

5.8 Discontinuation Syndrome

5.9 Risk of Clinically Significant Adverse Reactions due to Persistence of MAO Inhibition after Discontinuation

5.10 Hepatotoxicity

5.11 Seizures

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS AND HYPERTENSIVE CRISIS WITH SIGNIFICANT TYRAMINE USE

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* (5.1)]. Tranlycypromine sulfate is not approved for use in pediatric patients [see *Use in Specific Populations* (8.4)].

Hypertensive Crisis with Significant Tyramine Use

Excessive consumption of foods or beverages with significant tyramine content or the use of certain drugs with tranlycypromine sulfate or after tranlycypromine sulfate discontinuation can precipitate hypertensive crisis. Monitor blood pressure and allow for medication-free intervals between administration of tranlycypromine sulfate and interacting drugs. Instruct patients to avoid ingestion of foods and beverages with high tyramine content [see *Warnings and Precautions* (5.2) and *Drug Interactions* (7.1, 7.2)].

- 1 INDICATIONS AND USAGE
- Tranlycypromine Sulfate is indicated for the treatment of major depressive disorder (MDD) in adult patients who have not responded adequately to other antidepressants. Tranlycypromine Sulfate 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 [see *Contraindications* (4), *Warnings and Precautions* (5), and *Drug Interactions* (7)].
- 2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dosage
- Tranlycypromine Sulfate Tablets. USP are for oral use. The recommended dosage is 30 mg per day (in divided doses). If patients do not have an adequate response, increase the dosage in increments of 10 mg per day every 1 to 3 weeks to a maximum 30 mg twice daily (60 mg per day). Dosage increases should be made more gradually in patients at risk for hypotension (e.g., geriatric patients) [see *Warnings and Precautions* (5.5)].
- 2.2 Switching to or from Other Antidepressants
- Switching from Contraindicated Antidepressants to Tranlycypromine Sulfate
- After stopping treatment with contraindicated antidepressants, a time period of 4 to 5 half-lives of the other antidepressant or any active metabolite should elapse before starting treatment with tranlycypromine sulfate. After stopping treatment with an MAOI inhibitor antidepressant, a time period of at least one week or 4 to 5 half-lives of the other MAOI inhibitor (whichever is longer) should elapse before starting treatment with tranlycypromine sulfate to reduce the risk of additive effects [see *Contraindications* (4.1) and *Drug Interactions* (7.1)].
- Switching from Tranlycypromine Sulfate to Other MAOIs or Contraindicated Antidepressants
- After stopping tranlycypromine sulfate treatment, at least one week should elapse before starting another MAOI (intended to treat MDD) or other contraindicated antidepressants. Refer to the prescribing information of the subsequently used drug for product-specific advice on a medication-free interval [see *Contraindications* (4.1) and *Drug Interactions* (7.1)].
- 2.3 Discontinuing Treatment
- Withdrawal effects, including delirium, have been reported with abrupt discontinuation of tranlycypromine sulfate therapy. Higher daily doses and longer duration of use appear to be associated with a higher risk of withdrawal effects. Consider discontinuing tranlycypromine sulfate therapy by slow, gradual dosage reduction [see *Warnings and Precautions* (5.8) and *Drug Abuse and Dependence* (9.3)].

- Switching from or to other MAOIs or other antidepressants: See full prescribing information for instructions (2.2, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg (3)

CONTRAINDICATIONS

- Concomitant use or use in rapid succession with other MAOIs; selective serotonin reuptake inhibitors; serotonin and norepinephrine reuptake inhibitors; tricyclic antidepressants; sympathomimetic drugs; and numerous other drugs. See Full Prescribing Information for the full list of contraindicated products (4.1, 7.1)
- Pheochromocytoma, other catecholamine-releasing paraganglioma (4.2)

WARNINGS AND PRECAUTIONS

- Activation of Mania/Hypomania: May be precipitated by antidepressant treatment in patients with bipolar disorder. Screen patients prior to treatment (5.4)
- Hypotension (including syncope): Monitor patients and adjust tranlycypromine sulfate dosage or concomitant medication as necessary (5.5)
- Hypotension and Hypertension during Anesthesia and Perioperative Care: If possible, discontinue tranlycypromine sulfate prior to elective surgery (5.6)
- Hepatitis and Elevated Liver Enzymes: Monitor accordingly (5.10)

ADVERSE REACTIONS

Most common adverse reactions (>10%) were dry mouth, dizziness, insomnia, sedation, headache, overexcitement, constipation, blurred vision, and tremor (6)

To report SUSPECTED ADVERSE REACTIONS, contact Strides Pharma Inc at 1-877-244-9825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See Full Prescribing Information for a list of products, foods and beverages that can interact with tranlycypromine sulfate (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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- 5.12 Hypoglycemia in Diabetic Patients
- 5.13 Aggravation of Coexisting Symptoms of Depression
- 5.14 Adverse Effects on the Ability to Drive and Operate Machinery
- 6 ADVERSE REACTIONS
- 7 DRUG INTERACTIONS
- 7.1 Clinically Significant Drug Interactions
- 7.2 Tyramine-Containing Foods and Beverages
- 8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 9 DRUG ABUSE AND DEPENDENCE
- 9.2 Abuse
- 9.3 Dependence
- 10 OVERDOSAGE
- 10.1 Overdosage Symptoms, Signs and Laboratory Abnormalities
- 10.2 Overdosage Management
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION
- *Sections or subsections omitted from the full prescribing information are not listed.

2.4 Screen for Bipolar Disorder and Elevated Blood Pressure Prior to Starting Tranlycypromine Sulfate

- Prior to initiating treatment with tranlycypromine sulfate:
- Screen patients for a history of mania [see *Warnings and Precautions* (5.4)].
 - Measure blood pressure [see *Warnings and Precautions* (5.2, 5.5)].

3 DOSAGE FORMS AND STRENGTHS

Tablets containing tranlycypromine sulfate equivalent to 10 mg tranlycypromine are round, dark pink, film-coated, and debossed with "250" on one side and "K" on the other side.

4 CONTRAINDICATIONS

4.1 Combination with Certain Drugs

Concomitant use of tranlycypromine sulfate or use in rapid succession with the products in Table 1 is contraindicated. Such use may cause severe or life-threatening reactions such as hypertensive crises or serotonin syndrome [see *Drug Interactions* (7.1)]. Medication-free periods between administration of tranlycypromine sulfate and contraindicated agents are recommended [see *Dosage and Administration* (2.2) and *Drug Interactions* (7.1)].

Table 1: Products Contraindicated with the Use of Tranlycypromine Sulfate		
Drug Classes		
Non-selective H1 receptor antagonists		
Antidepressants including but not limited to:		
• Other monoamine oxidase inhibitors (MAOIs)		
• Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)		
• Tricyclic antidepressants		
• Other antidepressants (e.g., amoxapine, bupropion, maprotiline, nefazodone, trazodone, vilazodone, vortioxetine)		
Amphetamines and methylphenidates and derivatives		
Sympathomimetic products (e.g., cold, hay fever or weight-reducing products that contain vasoconstrictors such as pseudoephedrine, phenylephrine, and ephedrine; or dietary supplements that contain sympathomimetics)		
Triptans		
Individual Drugs (not included in the above classes)		
bupropion	levodopa	s-adenosyl-L-methionine (SAM-e)
carbamazepine	meperidine	tapentadol
cyclobenzaprine	methylodopa	tetrabenazine
dextromethorphan	milnacipran	tryptophan
dopamine	rasagiline	
hydroxytryptophan	reserpine	

4.2 Pheochromocytoma and Catecholamine-Releasing Paragangliomas

Tranlycypromine Sulfate is contraindicated in the presence of pheochromocytoma or other catecholamine-releasing paragangliomas because such tumors secrete pressor substances and can lead to hypertensive crisis [see *Warnings and Precautions* (5.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 2.

Table 2: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients		
Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated	
	Increases Compared to Placebo	
<18 years old	14 additional patients	
18 to 24 years old	5 additional patients	
	Decreases Compared to Placebo	
25 to 64 years old	1 fewer patient	
≥65 years old	6 fewer patients	

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing tranlycypromine sulfate, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Hypertensive Crisis and Hypertension

MAOIs, including tranlycypromine sulfate, have been associated with hypertensive crises caused by the ingestion of foods or beverages with a high concentration of tyramine. In addition, hypertensive reactions and crises may occur with concomitant use of other drugs [see *Drug Interactions* (7.1)]. Patients with hyperthyroidism may be at greater risk of hypertensive crisis.

Signs, Symptoms, and Complications of Hypertensive Crisis: In some patients a hypertensive crisis constitutes a hypertensive emergency, which requires immediate attention to prevent serious complications or fatal outcome. These emergencies are characterized by severe hypertension (e.g., with a blood pressure of more than 180/120 mm Hg) and evidence of organ dysfunction. Symptoms may include occipital headache (which may radiate frontally), palpitations, neck stiffness or soreness, nausea or vomiting, sweating (sometimes with fever or cold, clammy skin), dilated pupils, photophobia, shortness of breath, or confusion. Either tachycardia or bradycardia may be present and may be associated with constricting chest pain. Seizures may also occur. Intracranial bleeding, sometimes fatal, has been reported in association with the increase in blood pressure.

Strategies to Reduce the Risk of Hypertensive Crisis: Instruct patients to avoid foods and beverages with high tyramine content while being treated with tranlycypromine sulfate and for 2 weeks after stopping tranlycypromine sulfate [see *Drug Interactions* (7.2)]. Careful evaluation of the benefits and risks of tranlycypromine sulfate therapy is necessary in patients with:

- Hypertension or confirmed or suspected cerebrovascular or cardiovascular disorders that constitute an increased risk for complications from severe hypertension, and
- A history of headaches that can mask the occurrence of headaches as prodromal of a hypertensive crisis.

In all patients taking tranlycypromine sulfate, monitor blood pressure closely to detect evidence of increased blood pressure. Full reliance should not be placed on blood pressure readings. The patient should also be observed for other signs and symptoms of hypertensive crisis.

Treatment of Hypertensive Crisis: Therapy should be interrupted with symptoms that may be prodromal or a manifestation of a hypertensive crisis, such as palpitations or headaches, and patients should be evaluated immediately. Discontinue tranlycypromine sulfate, other drugs, foods or beverages suspected to contribute to the hypertensive crisis immediately [see *Drug Interactions* (7.1, 7.2)].

Patients with severe elevations in blood pressure (e.g., more than 180/120 mm Hg) with evidence of organ dysfunction require immediate blood pressure reduction. Fever should be managed by means of external cooling. However, additional measures to control the causes of hyperthermia (psychomotor agitation, increased neuromuscular activity, persistent seizures) may be required.

Hypotension

Clinically significant increases in blood pressure have also been reported after the administration of MAOIs, including tranlycypromine sulfate, in patients not ingesting tyramine-rich foods or beverages. Assess blood pressure before prescribing tranlycypromine sulfate and closely monitor blood pressure in all patients taking tranlycypromine sulfate.

5.3 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with MAOIs when used concomitantly with other serotonergic drugs. Such drugs include SSRIs, SNRIs, tricyclic antidepressants, triptans, fentanyl, tramadol, tryptophan, buspirone, St. John's wort, S-adenosyl-L-methionine (SAM-e), and other MAOIs used to treat nonpsychiatric disorders (such as linezolid or intravenous methylene blue).

Manifestations of the serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, delirium, coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia; with possible rapid fluctuations of vital signs), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyper-reflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Fatal outcome of serotonin syndrome has been reported, including in patients who had been treated with tranlycypromine sulfate. In some cases of an interaction between tranlycypromine sulfate and SSRIs or SNRIs, the features of the syndrome resembled neuroleptic malignant syndrome.

The concomitant use, or use in rapid succession, of tranlycypromine sulfate with other serotonergic drugs is contraindicated. However, there may be circumstances when treatment with other serotonergic substances (such as linezolid or intravenous methylene blue) is necessary and cannot be delayed. In such cases, tranlycypromine sulfate must be discontinued as soon as possible before initiating treatment with the other agent.

Treatment with tranlycypromine sulfate and any concomitant serotonergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

5.4 Activation of Mania or Hypomania

In patients with bipolar disorder, treating a depressive episode with tranlycypromine sulfate or another antidepressant may precipitate a manic episode. Prior to initiating treatment with tranlycypromine sulfate, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.

5.5 Hypotension

Hypotension, including postural hypotension, has been observed during therapy with Tranlycypromine Sulfate. At doses above 30 mg daily, postural hypotension is a major adverse reaction and may result in syncope. Symptoms of postural hypotension are seen most commonly, but not exclusively, in patients with pre-existing hypotension. Blood pressure usually returns rapidly to pretreatment levels upon discontinuation of tranlycypromine sulfate.

Dosage increases should be made more gradually in patients with a tendency toward hypotension and/or postural hypotension (e.g., elderly patients) [see *Dosage and Administration* (2.2) and *Use in Specific Populations* (8.5)]. Such patients should be closely observed for postural changes in blood pressure throughout treatment. Also, when tranlycypromine sulfate is used concomitantly with other agents known to cause hypotension, the possibility of additive hypertensive effects should be considered [see *Drug Interactions* (7.1)]. Postural hypotension may be relieved by having patients lie down until blood pressure returns to normal.

5.6 Hypotension and Hypertension during Anesthesia and Perioperative Care

It is recommended that tranlycypromine sulfate be discontinued at least 10 days prior to elective surgery. If this is not possible, for general anesthesia, regional and local anesthesia, and perioperative care avoid the use of agents that are contraindicated for concomitant use with tranlycypromine sulfate. Carefully consider the risk of agents and techniques that increase the risk for hypotension (e.g., epidural or spinal anesthesia) or other adverse reactions to tranlycypromine sulfate (e.g., hypotension associated with the use of vasoconstrictors in local anesthetics).

5.7 Need for Emergency Treatment with Contraindicated Drugs

If in the absence of therapeutic alternatives emergency treatment with a contraindicated product (e.g., linezolid, intravenous methylene blue, direct-acting sympathomimetic drugs such as epinephrine) becomes necessary and cannot be delayed, discontinue tranlycypromine sulfate as soon as possible before initiating treatment with the other product and monitor closely for adverse reactions [see *Drug Interactions* (7.1)].

5.8 Discontinuation Syndrome

Abrupt discontinuation or dosage reduction of tranlycypromine sulfate has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy.

There have been spontaneous reports of adverse reactions occurring upon discontinuation of MAOIs, particularly when abrupt, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these reactions are generally self-limiting, there have been reports of prolonged discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with tranlycypromine sulfate. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible [see *Dosage and Administration* (2.3) and *Adverse Reactions* (6)].

5.9 Risk of Clinically Significant Adverse Reactions due to Persistence of MAO Inhibition after Discontinuation

Although excretion of tranlycypromine sulfate is rapid, inhibition of MAO may persist up to 10 days following discontinuation. This should be taken into account when considering the use of potentially interacting substances or the consumption of tyramine-rich food or beverages [see *Drug Interactions* (7.4)], or when interpreting adverse reactions observed after discontinuation of tranlycypromine sulfate. Care should be taken to differentiate symptoms of persistent MAO inhibition from withdrawal symptoms [see *Drug Abuse and Dependence* (9.3)].

5.10 Hepatotoxicity

Hepatitis and elevated aminotransferases have been reported in association with tranlycypromine sulfate administration. Patients should be monitored accordingly. Tranlycypromine sulfate should be discontinued in patients who develop signs and symptoms of hepatotoxicity.

Sedation has occurred in tranlycypromine sulfate-treated patients with cirrhosis. Patients with cirrhosis receiving tranlycypromine sulfate should be monitored for possible increased risks of central nervous system adverse reactions, such as excessive drowsiness.

5.11 Seizures

Seizures have been reported with tranlycypromine sulfate withdrawal after abuse, and with overdose. Patients at risk for seizures should be monitored accordingly.

5.12 Hypoglycemia in Diabetic Patients

Some MAOIs have contributed to hypoglycemic episodes in diabetic patients receiving insulin or other blood-glucose-lowering agents. Monitor blood glucose in patients receiving both tranlycypromine sulfate and blood-glucose-lowering agents. A reduction of the dosage of such agents may be necessary [see *Drug Interactions* (7.1)].

5.13 Aggravation of Coexisting Symptoms of Depression

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

5.14 Adverse Effects on the Ability to Drive and Operate Machinery

Some tranlycypromine sulfate adverse reactions (e.g., hypotension, faintness, drowsiness, confusion, disorientation) can impair a patient's ability to operate machinery or use an automobile. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that tranlycypromine sulfate therapy does not impair their ability to engage in such activities.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Suicidal thoughts and behaviors [see *Warnings and Precautions* (5.1)]
- Hypertensive crisis and hypertension [see *Warnings and Precautions* (5.2)]
- Serotonin syndrome [see *Warnings and Precautions* (5.3)]
- Activation of mania/hypomania [see *Warnings and Precautions* (5.4)]
- Hypotension [see *Warnings and Precautions* (5.5)]
- Hypotension and hypertension during anesthesia and perioperative care [see *Warnings and Precautions* (5.6)]
- Discontinuation syndrome [see *Warnings and Precautions* (5.8)]
- Persistence of MAO inhibition after discontinuation [see *Warnings and Precautions* (5.9)]
- Hepatotoxicity [see *Warnings and Precautions* (5.10)]
- Seizures [see *Warnings and Precautions* (5.11)]
- Hypoglycemia in diabetic patients [see *Warnings and Precautions* (5.12)]
- Aggravation of coexisting symptoms of depression [see *Warnings and Precautions* (5.13)]
- Adverse effects on the ability to drive and operate machinery [see *Warnings and Precautions* (5.14)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Based on clinical trial data, the most common adverse reactions to tranlycypromine were dry mouth, dizziness, insomnia, sedation, and headache (>30%) and overexcitement, constipation, blurred vision, and tremor (>10%).

The following adverse reactions have been identified in clinical trials or during postapproval use of tranlycypromine sulfate: **Blood and lymphatic system disorders:** agranulocytosis, leukopenia, thrombocytopenia, anemia. **Endocrine disorders:** impaired water excretion compatible with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Metabolism and nutrition disorders: significant anorexia, weight gain

Psychiatric disorders: excessive stimulation/overexcitement, manic symptoms/hypomania, agitation, insomnia, anxiety, confusion, disorientation, loss of libido

Nervous system disorders: dizziness, restlessness/akathisia, akinesia, ataxia, myoclonic jerks, tremor, hyper-reflexia, muscle spasm, paresthesia, numbness, memory loss, sedation, drowsiness, dysgeusia, headaches (without blood pressure elevation)

Eye disorders: blurred vision, nystagmus

Ear and labyrinth disorders: tinnitus

Cardiac disorders: tachycardia, palpitations

Vascular disorders: hypertensive crisis, hypertension, hypotension (including postural hypotension with syncope)

Gastrointestinal disorders: diarrhea, constipation, nausea, abdominal pain, dry mouth, fissuring in corner of mouth

Hepatobiliary disorders: hepatitis, elevated aminotransferases

Skin and subcutaneous tissue disorders: localized scleroderma, flare-up of cystic acne, urticaria, rash, alopecia, sweating

Renal and urinary disorders: urinary retention, urinary incontinence, urinary frequency

Reproductive system and breast disorders: impotence, delayed ejaculation

General disorders and administration site conditions: edema, chills, weakness, fatigue/lethargy

7 DRUG INTERACTIONS

7.1 Clinically-Significant Drug Interactions

Tables 3 and 4 lists drug classes and individual products, respectively, with a potential for interaction with tranlycypromine sulfate, describes the predominant observed or anticipated risks, and provides advice on concomitant use. Given serious adverse reactions with multiple agents, patients should avoid taking over-the-counter medications or dietary supplements without prior consultation with a healthcare provider able to provide advice on the potential for interactions.

Time to Start Tranlycypromine Sulfate after Discontinuation of a Contraindicated Drug

For products that are contraindicated with tranlycypromine sulfate, a time period of 4 to 5 half-lives of the other product or any active metabolite should elapse before starting treatment with tranlycypromine sulfate. After stopping treatment with an MAOI inhibitor antidepressant, a time period of at least 1 week or 4 to 5 half-lives of the other MAOI inhibitor (whichever is longer) should elapse before starting treatment with tranlycypromine sulfate because of the risk for clinically significant adverse reactions after discontinuation due to persistent MAO inhibition [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.9)]. This period can be several weeks long (e.g., a minimum of 5 weeks for fluoxetine given fluoxetine's long half-life). Refer to the prescribing information of the contraindicated product for relevant information.

Time to Start Contraindicated Drug after Discontinuation of Tranlycypromine Sulfate

The potential for interactions persists after discontinuation of tranlycypromine sulfate until MAO activity has sufficiently recovered. Inhibition of MAO may persist up to 10 days following discontinuation [see *Warnings and Precautions* (5.9)]. After stopping tranlycypromine sulfate, at least 1 week should elapse before starting another MAOI (intended to treat MDD) or other contraindicated antidepressants. Refer to the prescribing information of any agent considered for subsequent use for recommendations on the duration of a waiting period after discontinuation of a MAO inhibitor.

If in the absence of therapeutic alternatives and emergency treatment with a contraindicated drug (e.g., linezolid, intravenous methylene blue, direct-acting sympathomimetic drugs such as epinephrine) becomes necessary and cannot be delayed, discontinue tranlycypromine sulfate as soon as possible before initiating treatment with the other agent, and monitor closely for adverse reactions.

Table 3: Clinically Significant Drug Interactions with Drug Classes*		
Product	Clinical Comment on Concomitant Use ^a	Predominant Effect/Risk [Hypertensive Reaction (HR) ^b or Serotonin Syndrome (SS)]

10 OVERDOSAGE

10.1 Overdose Symptoms, Signs, and Laboratory Abnormalities

Overdose of tranylcypromine sulfate can cause the adverse reactions generally associated with tranylcypromine sulfate administration [see *Warnings and Precautions* (5), *Adverse Reactions* (6) and *Drug Interactions* (7.1)]. However, these reactions may be more severe, including fatal reactions. Effects reported with overdose of tranylcypromine sulfate and/or other MAOIs include:

- Insomnia, restlessness, and anxiety, progressing in severe cases to agitation, mental confusion, and incoherence; delirium; seizures
- Hypotension, dizziness, weakness, and drowsiness, progressing in severe cases to extreme dizziness and shock
- Hypertension with severe headache and other symptoms/complications
- Twitching or myoclonic fibrillation of skeletal muscles, with hyperpyrexia, sometimes progressing to generalized rigidity and coma

10.2 Overdose Management

There are no specific antidotes for tranylcypromine sulfate. For current information on the management of poisoning or overdose, contact a poison control center at 1-800-222-1222.

Abrupt withdrawal of tranylcypromine sulfate following overdose can precipitate withdrawal symptoms, including delirium [see *Warnings and Precautions* (5.9) and *Drug Abuse and Dependence* (9.3)].

Medical management should normally consist of general supportive measures, close observation of vital signs, and steps to counteract specific manifestations as they occur [see *Warnings and Precautions* (5)]. The toxic effects of tranylcypromine sulfate may be delayed or prolonged following the last dose of the drug [see *Clinical Pharmacology* (12.2)]. Therefore, the patient should be closely observed for at least 1 week.

Data on the dialyzability of tranylcypromine are lacking.

11 DESCRIPTION

Tranylcypromine sulfate, the active ingredient of Tranylcypromine Sulfate Tablets, USP, is a non-hydrazone MAOI. The chemical name is (±)-trans-2-phenylcyclopropylamine sulfate (2:1). The molecular formula is (C₉H₁₁N)₂•H₂SO₄ and its molecular weight is 364.46. The structural formula is:



Tranylcypromine Sulfate film-coated tablets are intended for oral administration. Each round, dark pink, film-coated tablet is debossed with "250" on one side and "K" on the other side and contains tranylcypromine sulfate equivalent to 10 mg of tranylcypromine.

Inactive ingredients consist of colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate anhydrous, magnesium stearate, microcrystalline cellulose, talc, and Opadry® II pink 85F14289. Opadry pink is used for purposes of coating and contains the following: FD&C Red # 40, polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of tranylcypromine sulfate 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).

12.2 Pharmacodynamics

Although tranylcypromine is eliminated in 24 hours, recovery MAO activity takes up to 3 to 5 days [see *Warnings and Precautions* (5.9)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenesis, mutagenesis, or fertility impairment studies were conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tranylcypromine Sulfate Tablets, USP are supplied as round, dark pink, film-coated tablets debossed with "250" on one side and "K" on the other side and contains tranylcypromine sulfate equivalent to 10 mg of tranylcypromine, in bottles of 100 with a desiccant. Tranylcypromine Sulfate tablets are available as:

- 10 mg; bottles of 100 tablets: NDC 64380-176-01

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

[See USP Controlled Room Temperature].

Dispense in a tight, light resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidal thoughts and behaviors, especially early during treatment and when the dosage is adjusted up or down [see *Box Warning and Warnings and Precautions* (5.1)].

Hypertensive Crisis

Advise the patient on possible symptoms and instruct the patient to seek immediate medical attention if related signs or symptoms are present [see *Boxed Warning and Warnings and Precautions* (5.2)].

Serotonin Syndrome

Advise the patient on possible symptoms, and explain the potentially fatal nature of serotonin syndrome and that it may result from an interaction with other serotonergic drugs. Instruct the patient to seek immediate medical attention if related signs or symptoms are present [see *Warnings and Precautions* (5.3)].

Interaction with Other Drugs and Dietary Supplements [see *Contraindications* (4.1) and *Drug Interactions* (7.1)]

- Warn the patient not to take concomitant medications, whether prescription or over-the-counter drugs, or dietary supplements without prior consultation with a health care provider able to provide advice on the potential for interactions.

- Explain to the patient that some other drugs may require a medication-free interval even after discontinuation of tranylcypromine sulfate.

- Advise the patient to inform other physicians, pharmacists, and dentists about the treatment with tranylcypromine sulfate.

Interaction with Foods and Beverages [see *Contraindications* (4.1) and *Drug Interactions* (7.2)]

- Warn the patient to avoid tyramine-rich foods and beverages.

- Advise the patient to avoid eating foods if storage conditions or freshness is unknown and to be cautious of foods of unknown age or composition even if refrigerated.

Hypotension

Advise the patient to report any symptoms of hypotension in the initial phase of treatment to the healthcare provider, because occurrence of such symptoms may require discontinuation [see *Dosage and Administration* (2.1) and *Warnings and Precautions* (5.5)].

Withdrawal Symptoms

Warn the patient not to stop tranylcypromine sulfate treatment abruptly, as withdrawal symptoms may occur and that the effect of tranylcypromine sulfate may continue even after discontinuation [see *Warnings and Precautions* (5.8, 5.9)].

Aggravation of Coexisting Symptoms of Depression

Inform the patient that tranylcypromine sulfate may aggravate coexisting symptoms in depression, such as anxiety and agitation and instruct them to contact their healthcare provider if they experience such symptoms [see *Warnings and Precautions* (5.13)].

Effects on Ability to Drive or Use Machinery [see *Warnings and Precautions* (5.14)]

- Warn the patient about the possible adverse reactions that can impair the performance of potentially hazardous tasks such as driving a car or operating machinery.

- Tell the patient not to operate hazardous machinery and automobiles until they are reasonably certain that their ability to engage in such activities is not impaired.

MEDICATION GUIDE

Tranylcypromine Sulfate Tablets, USP
(TRAN-il-SIP-roe-meen suhl-feyt)

What is the most important information I should know about Tranylcypromine Sulfate tablets?

Tranylcypromine Sulfate tablets can cause serious side effects including:

- **Increase in suicidal thoughts or actions** in some children, teenagers, and young adults within the first few months of treatment and when the Tranylcypromine Sulfate dose is changed. 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. **Tranylcypromine Sulfate is not for use in children.**

How can I watch for and try to prevent suicidal thoughts and actions?

- 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 your 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 have any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worse depression
- feeling agitated, restless, angry or irritable
- trouble sleeping
- acting aggressive, being angry or violent
- an extreme increase in activity or talking (mania)
- attempts to commit suicide
- new or worse anxiety
- panic attacks
- new or worse irritability
- acting on dangerous impulses
- other unusual changes in behavior or mood

• **A sudden, severe increase in blood pressure (hypertensive crisis).**

A hypertensive crisis can happen when you eat certain foods and drink certain beverages during or after Tranylcypromine Sulfate treatment. A hypertensive crisis can lead to stroke and death. People who have thyroid problems (hyperthyroidism) may have a higher chance of having a hypertensive crisis. Symptoms of a hypertensive crisis may include:

- sudden, severe headache
- vomiting
- a fast heartbeat (palpitations) or a change in the way your heart beats
- the pupils in your eyes increase in size
- fast or slow heart beat with chest pain
- nausea
- stiff or sore neck
- excessive sweating, sometimes with fever or cold, clammy skin
- light bothers your eyes
- bleeding in your brain

A hypertensive crisis can also happen if you take Tranylcypromine Sulfate with certain other medicines. See, “Who should not take Tranylcypromine Sulfate?”

Avoid foods and drinks with a lot of tyramine while taking Tranylcypromine Sulfate and for 2 weeks after you stop taking it. For a list of some of the foods and drinks you should avoid during treatment with Tranylcypromine Sulfate see, “What should I avoid while taking Tranylcypromine Sulfate?”

What is Tranylcypromine Sulfate?

Tranylcypromine Sulfate is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder (MDD) who have not responded well to treatment with other medicines used to treat depression (antidepressants). Tranylcypromine Sulfate belongs to a class of medicines called monoamine oxidase inhibitors (MAOIs).

- It is important to talk with your healthcare provider about the risks of treating depression and the risk of not treating it. Talk with your healthcare provider about all your treatment choices.
- Tranylcypromine Sulfate is not for use as the first medicine to treat MDD.
- It is not known if Tranylcypromine Sulfate is safe and effective for use in children.

Who should not take Tranylcypromine Sulfate?

Taking Tranylcypromine Sulfate with certain antidepressants and certain pain, allergy symptom, and cold and cough symptom medicines may cause a potentially life-threatening hypertensive crisis or a problem called serotonin syndrome. See, “What is the most important information I should know about Tranylcypromine Sulfate?” and “What are the possible side effects of Tranylcypromine Sulfate?”

Do not take Tranylcypromine Sulfate if you:

- **take certain medicines, including:**
 - antidepressants, such as:
 - other monoamine oxidase inhibitors (MAOIs)
 - selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)
 - tricyclic antidepressants
 - other antidepressants, such as amoxapine, bupropion, maprotiline, nefazodone, trazodone, vilazodone, vortioxetine
 - amphetamines and methylphenidates

- medicines that can raise blood pressure (sympathomimetic medicine), such as pseudoephedrine, phenylephrine and ephedrine. These medicines are in some cold, hay fever or weight-loss medicines.
- sympathomimetic herbal medicines or dietary supplements
- antihistamines (allergy medicines)
- triptans
- buspirone
- carbamazepine
- dextromethorphan
- dopamine
- hydroxytryptophan and tryptophan
- levodopa and methylodopa
- meperidine
- rasagiline
- reserpine
- s-adenosyl-L-methionine (SAM-e)
- tapentadol
- tetrabenazine

Ask your healthcare provider or pharmacist if you are not sure if you take any of these medicines.

- **have a tumor on your adrenal gland called a pheochromocytoma or a type of tumor called a paraganglioma.**

Before taking Tranylcypromine Sulfate, tell your healthcare provider about all your medical conditions, including if you:

- have high or low blood pressure
- have heart problems
- have cerebrovascular problems or have had a stroke
- have headaches
- have, or have a family history of, bipolar disorder, mania or hypomania
- plan to have surgery
- have liver or thyroid problems
- have or have had seizures or convulsions
- have diabetes
- are pregnant or plan to become pregnant. Tranylcypromine Sulfate may harm your unborn baby.
- are breastfeeding or plan to breastfeed. Tranylcypromine Sulfate passes into your breast milk. Do not breastfeed during treatment with Tranylcypromine Sulfate. Talk to your healthcare provider about the best way to feed your baby while taking Tranylcypromine Sulfate.

Tell your healthcare provider about all medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Tranylcypromine Sulfate and some other medicines may affect each other causing serious side effects. Tranylcypromine Sulfate may affect the way other medicines work, and other medicines may affect how Tranylcypromine Sulfate works.

Some medicines need to be stopped for a period of time before you can start taking Tranylcypromine Sulfate and for a period of time after you stop taking Tranylcypromine Sulfate.

Know the medicines you take. Keep a list of them to show your healthcare providers, pharmacist, and dentist when you get a new medicine.

How should I take Tranylcypromine Sulfate tablets?

- Take Tranylcypromine Sulfate tablets exactly as your healthcare provider tells you to take it.
- Your healthcare provider may need to change your dose of Tranylcypromine Sulfate tablets until it is the right dose for you.
- Do not stop taking Tranylcypromine Sulfate tablets without first talking to your healthcare provider. Stopping Tranylcypromine Sulfate suddenly may cause withdrawal symptoms. See, “What are the possible side effects of Tranylcypromine Sulfate tablets?”
- Tell your healthcare provider if you think your condition has gotten worse during treatment with Tranylcypromine Sulfate tablets.
- If you take too much Tranylcypromine Sulfate tablets (overdose) call your healthcare provider or poison control, or go to the nearest hospital emergency room right away.

What should I avoid while taking Tranylcypromine Sulfate tablets?

- Do not eat foods or have drinks that have high amounts of tyramine while taking Tranylcypromine Sulfate tablets or for 2 weeks after you stop taking Tranylcypromine Sulfate tablets.
 - All foods you eat should be fresh or properly frozen.
 - Avoid foods when you do not know how those foods should be stored.
 - Ask your healthcare provider if you are not sure if certain foods and drinks contain tyramine.

The table below lists some of the foods and drinks you should avoid while you take Tranylcypromine Sulfate tablets.

Type of Food and Drink that contain Tyramine	
Meat, Poultry, and Fish	• air dried, aged and fermented meats, sausages, and salamis • pickled herring • any spoiled or improperly stored meat, poultry, and fish. These foods have a change in color, odor, or are moldy. • spoiled or improperly stored animal livers
Vegetables	• broad bean pods (fava bean pods)
Dairy (milk products)	• aged cheeses
Drinks	• all tap beers and other beers that have not been <u>pasteurized</u>
Other	• concentrated yeast extract (such as Marmite) • most soybean products (including soy sauce and tofu) • sauerkraut • over-the-counter supplements containing tyramine

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how Tranylcypromine Sulfate tablets affects you.
- You should not drink alcohol while taking Tranylcypromine Sulfate tablets.

What are the possible side effects of Tranylcypromine Sulfate tablets?

Tranylcypromine Sulfate tablets may cause serious side effects, including:

- **See “What is the most important information I should know about Tranylcypromine Sulfate tablets?”**
- **Serotonin Syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when you take Tranylcypromine Sulfate tablets with certain other medicines. See, “Who should not take Tranylcypromine Sulfate?” Symptoms of serotonin syndrome may include:
 - agitation, confusion
 - coma
 - changes in blood pressure
 - sweating
 - high body temperature (hyperthermia)
 - seizures
 - becoming unstable
 - seeing or hearing things that are not real (hallucinations)
 - rapid pulse
 - dizziness
 - flushing
 - fever
 - tremors, stiff muscles, or muscle twitching
 - nausea, vomiting, diarrhea

If you have any of these symptoms, call your healthcare provider or go to the nearest hospital emergency room right away.

- **Mania or hypomania** (manic episodes) in people who have a history of bipolar disorder.

- greatly increased energy
- racing thoughts
- unusually grand ideas
- talking more or faster than usual
- severe problems sleeping
- reckless behavior
- excessive happiness or irritability

- **Low blood pressure (hypotension)** including a drop in your blood pressure when you stand or sit up (postural hypotension). This can happen more often in people who have high blood pressure (hypertension) and when the Tranylcypromine Sulfate tablets dose is changed. Postural hypotension may cause you to feel dizzy and faint (syncope).
- **Changes in your blood pressure (hypotension or hypertension) during surgery and during the time around surgery (perioperative).** Taking Tranylcypromine Sulfate tablets with certain medicines used for anesthesia can cause hypotension or hypertension. If you plan to have surgery, tell your surgeon or the healthcare provider who will give you anesthesia that you take Tranylcypromine Sulfate tablets. Your healthcare provider should stop Tranylcypromine Sulfate tablets at least 10 days before you have surgery.
- **Withdrawal symptoms.** Talk with your healthcare provider before you stop taking Tranylcypromine Sulfate tablets. Symptoms of withdrawal may include:

- dizziness
- irritability and agitation
- anxiety
- confusion
- changes in your mood
- seizures
- nausea
- problems sleeping
- abnormal dreams
- electric shock sensation (paresthesia)
- hypomania
- headache
- diarrhea
- sweating
- tiredness
- ringing in your ears (tinnitus)

• **Liver problems**

- **Seizures (convulsions).** Seizures have happened in people who take too much Tranylcypromine Sulfate tablets.

- **Low blood sugar (hypoglycemia).** Hypoglycemia has happened in people with diabetes who take medicines to lower blood sugar. Talk with your healthcare provider about checking your blood sugar during treatment with Tranylcypromine Sulfate tablets. Tell your healthcare provider if your blood sugar gets low.

- **Worsening of symptoms that can happen with depression,** such as anxiety and agitation.

The most common side effects of Tranylcypromine Sulfate tablets include:

- dry mouth
- problems sleeping
- headache
- constipation
- shakiness (tremor)
- dizziness
- feeling sleepy
- overexcitement
- blurry vision

These are not all the side effects of Tranylcypromine Sulfate.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store Tranylcypromine Sulfate tablets?

- Store Tranylcypromine Sulfate tablets at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

- Store Tranylcypromine Sulfate tablets in a tight, light resistant container.

Keep Tranylcypromine Sulfate tablets and all medicines out of the reach of children.

General information about the safe and effective use of Tranylcypromine Sulfate tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take Tranylcypromine Sulfate tablets for a condition for which it was not prescribed. Do not give Tranylcypromine Sulfate tablets to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about Tranylcypromine Sulfate tablets that is written for health professionals.

What are the ingredients in Tranylcypromine Sulfate tablets?

Active Ingredient: tranylcypromine sulfate

Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate anhydrous, magnesium stearate, microcrystalline cellulose, talc, and Opadry® II pink 85F14289. Opadry pink is used for purposes of coating and contains the following: FD&C Red # 40, polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

Medication Guide available at:

www.strides.com/medication-guides

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For more information, contact Strides Pharma Inc at 1-877-244-9825

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

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