

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tranlycypromine 10 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of tranlycypromine (as tranlycypromine sulfate).

Excipient with known effect:

0.47 mg of Allura Red AC (E129) and 82.00 mg of lactose monohydrate per tablet.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

Pink to light pink, round (diameter 7 mm) biconvex coated tablets debossed with 'Y3' on one side and score line on other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tranlycypromine is indicated for the treatment of Major Depressive Episodes in adult patients when treatment with other types of anti-depressant medication has failed.

4.2 Posology and method of administration

Posology

Adults

Initially, 1 tablet in the morning and again in afternoon. If the response is not adequate after the first week add a further tablet at midday, and continue for at least a week. A dosage of 3 tablets a day should only be exceeded with caution. When a satisfactory response has been obtained, dosage may be reduced to maintenance level often of 1 tablet a day.

When given with a tranquillizer, the dosage of tranylcypromine is not affected when given concurrently with electroconvulsive therapy; the usual dosage is 10 mg twice a day during the series and 1 tablet a day afterwards as maintenance therapy.

Elderly (over 65 years):

In elderly patients, tranylcypromine should be used with particular caution and initiated at the lowest dose (10 mg/day) and the dose may be increased weekly with regular monitoring of blood pressure by no more than 10 mg/day (see section 4.4).

Renal impairment

Patients with impaired renal function must be carefully monitored. Patients with severe disorders of renal function should not be treated with tranylcypromine (see section 4.4).

Hepatic impairment

Tranylcypromine is contraindicated in patients with impaired hepatic function (see section 4.3).

Paediatric population:

Tranylcypromine is not indicated for children and adolescents under 18 years of age.

Method of administration:

Oral use

Tablets should be swallowed whole with a glass of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Do not give tranylcypromine until at least two weeks after stopping treatment with other MAOIs.

Allow 3 weeks to elapse after stopping tranylcypromine before starting clomipramine or imipramine.

Tranylcypromine should not be taken by patients suffering from porphyria.

Tranylcypromine is contraindicated in patients with impaired hepatic function.

Do not give tranylcypromine with indirectly acting sympathomimetic amines such as amphetamine, fenfluramine or similar anti-obesity agents, ephedrine or phenylpropanolamine (certain cold cures may contain such agents) or with levodopa or dopamine, as severe hypertensive reactions may result; with pethidine and closely related narcotic analgesics, and nefopam, as potentiation may occur; with dextromethorphan as a similar reaction has been reported; with other MAO Inhibitors, as symptoms of overdosage are possible; or with buspirone, since increased blood pressure may occur.

Reports of hyperactivity, hypertonicity, hyperpyrexia, coma and death have been associated with the use of tranylcypromine in combination with tricyclic antidepressants; Tetracyclic antidepressants should also be avoided. The use of clomipramine in patients already on tranylcypromine may be particularly hazardous. Use of MAO inhibitors with or after fluvoxamine has been reported to produce a serotonin syndrome, sometimes fatal.

Do not use tranylcypromine in patients with actual or suspected cerebrovascular disease or severe cardiovascular disease; in those with actual or suspected phaeochromocytoma, or with hyperthyroidism; or blood dyscrasias.

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). 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 until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

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

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

Use tranylcypromine with great caution in patients with cardiovascular disease in whom physical activity should be regulated, as the drug may suppress angina pain.

Elderly patients

When treating elderly patients, the daily dose should be increased more slowly, with regular monitoring of blood pressure. The administered daily doses should be kept as low as possible (see section 4.2).

Patients with renal impairment:

There is insufficient experience with tranylcypromine in the treatment of patients with impaired renal function. Therefore, patients with severe disorders of renal function should not be treated with tranylcypromine. Other patients with impaired renal function should be closely monitored (see section 4.2).

Tyramine-rich food must not be consumed by patients on MAO inhibitor therapy, which is the cause of severe hypertensive reactions (see section 4.5 'Dietary precautions').

Also use tranylcypromine with great caution in epileptic patients, as tranylcypromine has a variable effect on the convulsive threshold in animals.

Tranylcypromine may aggravate some co-existing symptoms in depression such as anxiety and agitation.

Tranylcypromine should preferably be withdrawn at least two weeks before elective surgery because of possible drug interactions.

It is not recommended for mild depressive states resulting from temporary situational difficulties.

Caution should be exercised in prescribing tranylcypromine for patients with a previous history of dependence on drugs or alcohol.

Tranylcypromine therapy should be withdrawn gradually.

Tranylcypromine tablets contain lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Tranylcypromine 10 mg Tablets contains Allura Red AC (E129), which may cause allergic reaction.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should be specifically asked if they are taking any other medication because of the possibility of drug interactions.

Caution should be exercised when giving tranylcypromine with the following:

- guanethidine, as its action may be antagonised;
- reserpine, as hyperactivity may occur;
- methyldopa, as central excitation may result;

- other hypotensive agents because of possible additive effects;
- oral hypoglycaemic agents or insulin, as their action may be potentiated;
- anticholinergic antiparkinsonism drugs, as potentiation has been reported,
- narcotic analgesics, except pethidine which is contra-indicated (see above), because of possible potentiation; and carbamazepine, which has similarities with tricyclic antidepressants.

Metrizamide should be avoided in patients on MAO Inhibitors since they may lower the seizure threshold.

Although MAO Inhibitors have been used therapeutically with L-tryptophan. A neuromotor syndrome has been reported with this combination.

Exercise caution when giving tranylcypromine under following conditions:

- In combination with other monoamine oxidase inhibitors (MAOI). Avoid for at least 2 weeks after stopping previous MAOI (for e.g. furazolidone, isocarboxazid, pargyline HCl and procarbazine HCl) and then start at a reduced dose. Similarly, at least a week should elapse between the discontinuance of tranylcypromine and the administration of another MAOI, or the re-administration of tranylcypromine. Hypertensive crises or severe convulsive seizures may occur in patients receiving such combinations.
- In combination with selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline since CNS effects of SSRI may be potentiated. Serious and even fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation leading to delirium and coma) in patients receiving Fluoxetine in combination with a MAOI, and in patients who have recently discontinued Fluoxetine and are then started on a MAOI. There also have been cases presented with features resembling neuroleptic malignant syndrome. These drugs should not be given together or within 2 weeks of treatment with either drug. MAOIs should not be started until at least 5 weeks after starting Fluoxetine, since Fluoxetine and its major metabolite have very long elimination half-lives.
- In combination with tricyclic antidepressants, due to increased risk of hypertension and CNS excitation. After stopping tranylcypromine, do not start tricyclic related antidepressants (including amitriptyline, carbamazepine or trimipramine) for 2 weeks, also MAO inhibitors should not be started until at least 1-2 weeks (3 weeks in case of clomipramine or imipramine) after stopping tricyclic antidepressants.
- In combination with other antidepressants, due to increased risk of hypertension. At least 10 days should elapse between the discontinuation of MAOI and the start of Buspirone HCl.
- In combination with sympathomimetic drugs including amphetamine, ephedrine, phenylpropanolamine and over-the-counter cough & cold, hay fever or weight reducing preparations containing vasoconstrictors, guanethidine, methyl dopa, dopamine, levodopa and reserpine due to the risk of hypertensive crisis, headache and related symptoms. MAOIs in combination with tryptophan have been reported to cause behavioural and neurologic syndromes including disorientation, confusion, amnesia, delirium, agitation, hypomanic signs, ataxia, myoclonus, hyperreflexia, shivering, ocular oscillations and Babinski's signs.
- In combination with anticholinergic anti-parkinsonism drugs. Anti-parkinsonism drugs should be used with caution in patients receiving MAOIs.

- In combination with bupropion. The concurrent administration of bupropion and a MAOI is contraindicated. At least two weeks should elapse between discontinuation of a MAOI and initiation of treatment with bupropion HCl.
- Avoid concomitant use with opioid analgesics as possible CNS excitation or depression (hypertension or hypotension) may occur. Wait until two weeks after stopping MAOIs before starting treatment with opioid analgesics.
- In combination with antiepileptics, since MAOIs possibly antagonize anticonvulsant effects of antiepileptics (convulsive threshold lowered).
- In combination with antihistamines, since antimuscarinic and sedative effects of antihistamines are increased by MAOIs.
- Use of MAOIs may enhance the effects of barbiturates and possibly other hypnotics, hypoglycaemics, and possibly antimuscarinic agents.
- In surgery. Patients taking MAOIs should not undergo surgery requiring general anaesthesia. Also, they should not be given cocaine or local anaesthesia containing vasoconstrictors. The possible combined hypotensive effects of MAOIs and spinal anaesthesia should be kept in mind. Discontinue MAOI therapy two weeks before surgery because of the possible hazardous interaction with certain anaesthetics.

Dietary Precautions:

High levels of tyramine in certain foods have been the cause of severe hypertensive reactions in patients on MAO inhibitor therapy (See adverse reactions). Accordingly, patients must be warned to avoid the following: Matured cheeses, hydrolysed protein extracts such as Marmite or Bovril, alcoholic drinks, particularly red wines such as chianti, non-alcoholic beer and lager, and protein foods that are not fresh or whose preparation involved hydrolysis, fermentation, pickling or hanging, also broad bean pods which contain levodopa and banana skins.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of tranylcypromine in pregnant women. Animal studies are insufficient with respect to reproduction toxicity. Tranylcypromine should not be used in pregnancy, unless considered essential by the physician.

Breast-feeding

The drug is excreted in human milk and has been also found to pass into the milk in lactating dogs. A risk to the suckling child cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from tranylcypromine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No fertility data is available.

4.7 Effects on ability to drive and use machines

Tranlycypromine may affect the ability to drive and operate machinery. Patients should not undertake such activities unless it has been shown not to affect mental or physical capacity.

4.8 Undesirable effects

The following undesirable effects may occur with the use of Tranlycypromine in the following frequencies:

Rare ($\geq 1/10,000$ to $< 1/1,000$);

Not known (cannot be estimated from the available data).

The following effects have been reported and are listed below by body system:

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Rare	Blood dyscrasias
Psychiatric disorders	Rare	Hallucinations Hypomanias Drug dependence ¹
	Not known	Insomnia ² Anxiety Agitation, Suicidal ideation ⁶ Suicidal behaviours ⁶ Restlessness
Nervous system disorders	Rare	Paraesthesia Peripheral neuritis
	Not known	Dizziness Somnolence Headache Sleep disturbances Throbbing headache ⁵
Eye disorders	Not known	Vision blurred
Cardiac disorders	Not known	Palpitations
Vascular disorders	Not known	Orthostatic hypertension ³ Hypertensive crisis ⁴
Gastrointestinal disorders	Not known	Dry mouth, Diarrhoea Nausea Vomiting
Hepatobiliary disorders	Rare	Hepatocellular injury Jaundice
Skin and subcutaneous tissue	Not known	Rash

disorders		
General disorders and administration site conditions	Rare	Tolerance ¹
	Not known	Fatigue Weight gain Fluid retention

1 Dependence on tranlycypromine with tolerance to high doses has been reported rarely and can occur in patients without past history of drug dependence. This should be distinguished from the return of features of the original illness on cessation of treatment.

2 Insomnia is the most frequent side effect; it may usually be overcome by giving the last dose of the day not later than 3 p.m., by reducing dosage, or by prescribing a mild hypnotic.

3 Postural hypertension (which is usually temporary, but if it persists the drug should be stopped).

4 Severe hypertensive reactions may occur, notably in association with foods containing tyramine (see section 4.5). On occasions these have been fatal. Symptoms may be pain and stiffness in the neck, multiple extrasystoles, often with substernal pain, sweating and pallor, sometimes followed by flushing, mydriasis and photophobia.

5 Throbbing headache may be an early warning of hypertensive crisis.

6 Cases of suicidal ideation and suicidal behaviours have been reported during tranlycypromine therapy or early after treatment discontinuation (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Signs and symptoms are usually of the type already described as adverse reactions, but may be more intense, may include hyperpyrexia, tremor and convulsions, and may follow a latent period.

Management

Treatment consists of the induction of vomiting and/or gastric lavage together with supportive and symptomatic measures. External cooling is recommended for hyperpyrexia. Treat hypotension with fluid replacement; if severe or persistent, noradrenaline may be considered. Hypertension, if it occurs, may be relieved by slow intravenous injection of phentolamine mesylate. Pancuronium with mechanical ventilation may help reverse muscle spasm and pyrexia. Beta- Adrenergic receptor blockade has been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidepressants, non-selective monoamine oxidase inhibitors,
ATC code: N06AF04

Tranlycypromine is a non-Hydrazine monoamine oxidase inhibitor.

5.2 Pharmacokinetic properties

Absorption

Tranlycypromine is well and rapidly absorbed after oral administration.

Distribution

Peak plasma levels are reached after about 2.5 hours and the half-life is of the order of 2 hours.

Biotransformation

Tranlycypromine undergoes considerable metabolism, including breakdown of the side chain and probably conjugation. The main action of this compound is irreversible inhibition of MAO (both MAOA and MAOB) this lasts for some time, and clinically is considered to have reversed within 14 days.

Elimination

Excretion is pH dependent

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline

Croscarmellose sodium
Silica colloidal anhydrous
Magnesium stearate
Coating material (polyvinyl alcohol, macrogol, Titanium dioxide (E171), talc (E553b), Allura red
Aluminum lake (E129))

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

2 years

For Blister Pack: Use within 30 days after first opening of pouch.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

For Blister Pack: Store the blister in the original aluminium pouch with desiccant to protect from moisture. The desiccant is not for ingestion.

For Bottle Pack: Store in the original bottle to protect from moisture and keep the bottle tightly closed.

6.5 Nature and contents of container

Blister pack: White Opaque PVC/PVDC-Aluminium blister packs in aluminium pouch with molecular sieve as desiccant further packed in cardboard cartons. Pack sizes include 10, 20 and 30 film-coated tablets.

Container pack: HDPE containers with child resistant closures containing molecular sieve as desiccant. Pack size includes 28 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Europe Limited,
Laxmi House, 2 B Draycott Avenue,
Kenton, Middlesex, HA3 0BU,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0313

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

25/07/2022

10 DATE OF REVISION OF THE TEXT

25/07/2022