SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Abbonate 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains tranylcypromine sulfate equivalent to 20 mg tranylcypromine.

Excipient with known effect:
Each tablet contains 0.3 mg Ponceau 4R (E 124).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Red, round (diameter approx. 9 mm), convex tablet with a V-shaped score line on one side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of severe depressive episodes in adults with treatment resistant major depressive disorder where adequate treatment with two standard antidepressants (including tricyclic antidepressants) and augmentation with, e.g. lithium, yielded an insufficient treatment response.

4.2 Posology and method of administration

Treatment should only take place under medical supervision of a psychiatrist.

The patient should be provided with dietary advice by a dietician with knowledge of psychiatric diseases and the potential for food interactions with the medicinal product since tyramine-rich food should be avoided (see section 4.5).

A treatment-free period is required when switching from certain other antidepressants to Abbonate or vice versa (see sections 4.4 and 4.5). The treatment-free period should be at least five times the half-life of the other medical product and the active metabolites and should generally last for at least 7 days. If a switch is made from Abbonate to another therapy that is not compatible with tranylcypromine the treatment-free period should be 14 days. Upon starting Abbonate, only 10 mg/day should be prescribed for the first week of treatment. When switching from fluoxetine to Abbonate, the treatment-free period should be 4 weeks (see section 4.5). It is recommended to consult the product information, section 5.2, of the concerned products for the required treatment-free period.

The tablet should be swallowed whole or divided with a glass of water.

The total daily dose may, if needed, be divided into 2 to 3 doses per day (see section 4.4). The first dose should be taken in the morning. The last dose of the day should be taken at lunch time and at the latest at 3 pm to avoid sleep disturbances.

The recommended starting dose is 10 mg tranylcypromine once daily in the morning.

The dose is adjusted individually based on the patient response and the severity of the disease. If necessary, the daily dose may after 1-3 weeks be increased by 10 mg tranylcypromine depending on the effect *and with frequent monitoring of standing and supine blood pressure*.

Usually, the effective dose is 20–40 mg/day. If the therapeutic response is inadequate, the daily dose can be further increased with another 10 mg on a weekly basis up to a maximum daily dose of 60 mg/day and guided by the occurrence of adverse reactions. The antidepressive effect is generally achieved after a treatment duration of 3 to 6 weeks, but it may take longer depending on dosage and titration.

After reaching a sufficient response regarding the depressive symptoms, treatment with Abbonate should be continued for 4 to 6 months to prevent a relapse. A maintenance dose of 20–40 mg/day is sufficient in many cases, but if the depression recurs after a dose reduction a maintenance dose of 50-60 mg/day may be necessary.

A daily dose higher than 60 mg is not recommended since the available safety data are insufficient.

Sudden withdrawal of prolonged treatment with Abbonate should be avoided as this may lead to withdrawal symptoms such as anxiety, restlessness, insomnia, drowsiness, or delirium (see section 4.8). Treatment should therefore be discontinued by slow reduction in dose over a period of at least two weeks.

Paediatric population
Abbonate is contraindicated in children and adolescents younger than 18 years (see section 4.3).

Elderly (over 65 years)
In elderly patients, the lowest dose (10 mg/day) should be initiated, and the dose may be increased weekly with no more than 10 mg/day and with frequent monitoring of blood pressure (see section 4.4).

Patients with renal impairment
There is insufficient experience with the use of Abbonate in the treatment of patients with impaired renal function. Therefore, patients with severe renal impairment should not be treated with Abbonate (see section 4.3). Other patients with impaired renal function should be carefully monitored (see section 4.4).

Patients with hepatic impairment
Abbonate is contraindicated in patients with impaired hepatic function (see section 4.3).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pheochromocytoma
- Carcinoid tumours
- Suspected or recent history of cardiovascular event
- Vascular malformations such as aneurysms
- Hypertension or cardiovascular diseases that are severe and difficult to control
- Hepatic impairment or liver disease
- Severe renal impairment or renal disease
- Porphyria
- Diabetes insipidus

- Malignant hyperthermia, history of malignant hyperthermia
- Acute delirium
- Acute intoxication with CNS depressant medicinal products (i.e. sedatives, analgesics, and psychotropic drugs such as antipsychotics, antidepressants, lithium) and alcohol
- Concomitant use with:
  - Medicinal products with a strong serotonin reuptake inhibition, like all selective serotonin reuptake inhibitors (SSRI's, such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and selective serotonin-noradrenaline-reuptake inhibitors (SNRI's such as venlafaxine and duloxetine).
  - Tricyclic antidepressants (such as clomipramine, imipramine, amitriptyline, desipramine, nortriptyline and protriptyline)
  - Other MAO inhibitors (such as phenelzine)
  - Serotonin agonists like triptans for the treatment of migraine
  - Buspirone
  - Sympathomimetics (e.g. in medicinal products that increase blood pressure, and in certain nasal, cough or flu medicinal products and medicinal products for ADHD)
  - Pethidine, tramadol, dextromethorphan (dextromethorphan available in antitussives).
- Use in children and adolescents younger than 18 years.

4.4 Special warnings and precautions for use

Patients with blood pressure problems
Patients with moderately elevated or low blood pressure or patients at increased risk of hypertensive reactions (e.g. hyperthyroidism) should only use Abboante with frequent monitoring of blood pressure.
If the blood pressure before treatment is deviating from the normal, the risk of additional impact on the blood pressure should be outweighed towards the potential benefit of Abbonate. Abbonate should not be prescribed to patients with a cardiovascular risk (see section 4.3).
Ortostatic reactions with hypotension are very common and may motivate a divided dose, dose reduction or change of medicinal product.

Food and drink
Food and drinks that are rich in tyramine should not be consumed from the day that treatment is started until 14 days after treatment with Abbonate (see section 4.5).

Patients with psychiatric co-morbidity
Some effects of medicinal products for depression may be similar to symtoms of psychiatric diseases. Abbonate may aggravate current symptoms such as anxiety and agitation. In the event of episodes of mania Abbonate should be discontinued immediately (see section 4.8). The same applies in the event of (aggravation or existing) psychotic symptoms in patients with depressive episodes with psychotic features.

Special caution should be exercised in patients with a history of drug- or alcohol abuse.

Suicide / suicidal thoughts or clinical worsening
Tranylcypromine is characterised by a significant acute toxicity when overdosed (see section 4.9). This should also be considered when prescribing to patients with a suicidal risk.

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This increased risk persists, until there is a significant relief of symptoms. As improvement may not occur during the first few weeks of treatment, patients should be closely monitored until such improvement occurs. The general clinical experience shows that the risk of suicide may increase at initiation of treatment.

In patients with a history of suicidal behaviour or those that had pronounced suicidal ideation before treatment, the risk of suicidal thoughts is increased. These patients should therefore be carefully

monitored 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 younger than 25 years.

Close supervision of patients and in particular those at high risk of suicide 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 suicidal thoughts and unusual changes in behaviour. Immediate medical advice should be sought if these symptoms occur.

Serotonin syndrome
Serotonin syndrome, a potentially life-threatening condition, may occur with tranylcypromine treatment. This is particularly the case with concomitant use of other medicinal products that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, St. John's Wort (*Hypericum perforatum*), fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone, pentazocine, buprenorphine and naloxon) or medicinal products that may affect the metabolism of serotonin (including MAOIs e.g. methylene blue), with precursors of serotonin (such as tryptophan supplements), or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.5).

Symptoms of serotonin syndrome may include changes in mental status (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular disorders (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea).

Serotonin syndrome in its most severe form can resemble neuroleptic malignant syndrome. This includes symptoms such as hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuations of vital signs and changes in mental status.

If concomitant treatment with tranylcypromine and other medicinal products that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, it is recommended to perform careful observation of the patient, particularly during treatment initiation and dose increase (see sections 4.3 and 4.5). The concomitant use of tranylcypromine with precursors of serotonin (such as tryptophan supplements) is not recommended (see sections 4.3 and 4.5).

Patients with epilepsy
Abbonate may lower the seizure threshold. Therefore, Abbonate needs to be used with caution in patients with a history of seizures.

Patients with diabetes mellitus
In patients with diabetes, treatment with Abbonate may affect blood sugar. The dosage of insulin and/or oral hypoglycemic medicinal products may need to be adjusted (see section 4.5).

Patients with renal impairment
There is insufficient experience with the use of Abbonate in the treatment of patients with impaired renal function. Therefore, patients with severe renal impairment (GFR <30 mL / min and patients undergoing dialysis) should not be treated with Abbonate (see section 4.3). Other patients with impaired renal function should be carefully monitored (see section 4.2).

Patients with hepatic impairment
Abbonate is contraindicated in patients with hepatic impairment (see section 4.3).

Elderly
The elderly is generally more sensitive to orthostatic hypotension.

When treating elderly patients, the 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).

Excipients
Abbonate contains Ponceau 4R (E 124) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products influencing the effect of tranylcypromine
Abbonate should not be taken together with the following medicinal products (see section 4.3):
- medicinal products with strong serotonin reuptake inhibition, such as all selective serotonin reuptake inhibitors (SSRIs, such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), selective serotonin-and-noradrenaline reuptake inhibitors (SNRIs such as venlafaxine and duloxetine) and other serotonergic medicinal products (buprenorphine, naloxone) (risk of provoking serotonin syndrome with symptoms such as hypertension, irritability, hyperthermia, some with fatal outcome).
- tricyclic antidepressants (such as clomipramine, imipramine, amitriptyline, desipramine, nortriptyline and protriptyline) (risk of serotonin syndrome).
- other MAO inhibitors (such as phenelzine) (a sharp rise in blood pressure has been reported). When switching from another MAO inhibitor to Abbonate or vice versa, a treatment-free period of at least 7 days should generally be observed and only 10 mg/day should be prescribed in the first week of treatment with tranylcypromine.
- serotonin agonists such as triptans for the treatment of migraine (risk of serotonin syndrome).
- buspirone (a sharp rise in blood pressure has been reported).
- sympathomimetics, for example, medicinal products that increase blood pressure, as well as in certain nasal, cough, or flu medicines (risk of the occurrence of a severe hypertensive crisis) as well as medicinal products for ADHD
- pethidine, tramadol, dextromethorphan (present in cough antitussives) (life-threatening adverse CNS reactions or life-threatening effects on the respiratory and circulatory function are possible).

The extremely low concentrations of adrenalin or noradrenalin in local anaesthetics (e.g. dental procedures) or in eye drops do not represent a particular risk for patients treated with tranylcypromine because of the alternative pathway via the catechol-O-methyltransferase. The combination with selective $beta_2$-agonists for inhalation use is also not associated with any particular risk.

It has been reported that the combination of MAO inhibitors and tryptophan may cause behavioural and neurological symptoms.

Tranylcypromine influencing the effect of other medicinal products
The antihypertensive effect of blood pressure lowering medicinal products (e.g. guanethidine, methyldopa) may be enhanced by Abbonate. In some cases, an increase in blood pressure may be seen with agitation.

The effect of insulin and oral antidiabetic medicinal products may be enhanced (see section 4.4).

Side effects of bupropion, such as epileptic seizures and agitation may be exacerbated by concomitant treatment of Abbonate. This combination should therefore be avoided.

The sedative effect of centrally acting medicinal products (neuroleptics, antidepressants, benzodiazepines) may be enhanced with concurrent use of Abbonate (see also section 4.3).

Interactions during surgery and dental treatment
14 days before a planned surgical procedure using anaesthetics or certain analgesics, discontinuation of Abbonate should be considered, as interactions of irreversible MAO inhibitors (e.g. tranylcypromine) has been reported with anaesthetics, which in some cases were serious (unstable circulation, comatose states). Pethidine, a strong analgesic used e.g. in postoperative pain therapy should not be administered to patients using tranylcypromin (see section 4.3).

The possibility of overstimulation of the sympathetic nervous system is always present in patients treated with Abbonate.

Inhalation anaesthetics, except for ether, pose no additional risk, beyond the basic risk of the inhalation anaesthetics themselves.

These interactions are also valid for short-term use of the medicinal products listed above.

Interactions with food (see section 4.4)
Patients treated with MAO inhibitors should pay close attention to the intake of biogenic amines (tyramine and phenylethylamine) from the start of treatment until 14 days after treatment discontinuation. During treatment with MAO inhibitors, side effects (especially changes in blood pressure) are already possible from significantly low levels of tyramine (6 mg) and phenylethylamine (1 mg) per meal.

Serious increase in blood pressure which may be fatal is an expected reaction when ingesting 25 mg of tyramine per meal by a patient being treated with MAO inhibitors.

The proportion of tyramine that is absorbed is relative high with small meals and with concurrent use of alcohol. Biogenic amines may accumulate in food through microbial metabolic processes: in a normal fermentation process during the production process, but also by warm storage or damaged packaging material.

All foods should therefore be used as fresh as possible. The following product groups have a high tyramine content and should therefore be avoided: all blue and ripened cheeses; alcoholic beverages (in particular red wine); beer (even non-alcoholic); protein-rich food that are not fresh or whose preparation involved hydrolysis, fermentation, brining or drying; pickling or hanging, ripened meat; fish and poultry; all fermented soy products; sauerkraut; broad beans; concentrated yeast extracts, banana peel.

The effects of alcohol may be enhanced with concomitant use of Abbonate.

Dietary advice should be discussed with the patient by a dietician who has knowledge of psychiatric diseases and the food interactions of the medicinal product since tyramine rich food should be avoided.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Abbonate is not recommended to women of childbearing potential who are not using contraception. Patients of childbearing potential who is prescribed Abbonate, should be advised to contact their doctor immediately if they wish to become pregnant or if a pregnancy is suspected in order to be switched to another medicine.

Pregnancy
There are no adequate data from the use of Abbonate in pregnant women. Likewise, there are no adequate animal studies on reproductive toxicity of tranylcypromine (see section 5.3). Negative effects of tranylcypromine in pregnancy are possible due to reduced blood flow of the uterus and placenta. Abbonate is not recommended during pregnancy.

Breast-feeding
Abbonate is excreted in breast milk. Breastfeeding during treatment with Abbonate entails risks for the breastfeeded child. Abbonate should not be used during breast-feeding. If use of Abbonate is clearly necessary breastfeeding should be discontinued.

Fertility
There are no data on the effects of tranylcypromine on fertility.

4.7 Effects on ability to drive and use machines

Abbonate has minor or moderate influence on the ability to drive and use machines.

This applies to a greater extent with consumption of alcohol and/or in combination with other substances acting on the central nervous system. Therefore, at the start of the treatment, patients should not drive a car or other vehicles, use any electrical tools or machinery, or perform other potentially hazardous activities. With further experience of the individual patients reaction to tranylcypromine during the course of treatment, ability to drive and use machines can be determined.

4.8 Undesirable effects

Abbonate should be discontinued immediately in the occurrence of a manic episode (see section 4.4).

The following side effects can be expected very often, especially at the beginning of treatment: sleep disturbances, hypotension, orthostatic reactions (orthostatic hypotension).

Tabulated listing of adverse reactions

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders				Anaemia, leukopenia, neutropenia, agranulocytosis, thrombocytopenia		
Psychiatric disorders		Anxiety, agitation, restlessness		Psychological dependence	Hallucinations, confusion	Suicidal ideation, suicidal behaviour[1]
Nervous system disorders	Insomnia, sleep disturbances	Dizziness, dry mouth, fatigue		Epileptic seizures	Polyneuropathy	Drowsiness, tremor
Eye disorders					Accommodation disturbances	
Ear and labyrinth disorders						Tinnitus
Cardiac disorders		Palpitations				
Vascular disorders	Hypotension, orthostatic reaction (orthostatic hypotension)		Hypertension[2], intracranial bleeding[3]	Oedema		

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Gastrointestinal disorders				Constipation, diarrhoea		Nausea, with or without vomiting, non-specific gastro-intestinal symptoms
Hepatobiliary disorders					Liver dysfunction, increased liver enzyme activity	
Skin and subcutaneous tissue disorders				Sweating	Hair loss, allergic skin rashes	
Musculoskeletal and connective tissue disorders				Muscle spasms, muscle pain	Joint pain	
Renal and urinary disorders					Decreased urine production, correlating with syndrome of inappropriate ADH secretion	Dysuria
Reproductive system and breast disorders				Anorgasmia, erectile dysfunction, abnormal ejaculation		
General disorders and administration site conditions		Weight gain, weight loss, weakness			Hyper-thermia	Chest pain, cold sensations, exhaustion

[1] Cases of suicidal ideation during treatment with medicinal products containing the same active ingredient as Abbonate 20 mg film-coated tablets, or shortly after treatment discontinuation (see section 4.4).
[2] Hypertension to hypertensive crises with tachycardia, flushing, headache (especially occipital headaches), neck stiffness, vomiting and photophobia.
[3] Intracranial bleeding, particularly if the dietary requirements are not observed (see section 4.4) or in the event of drug interactions (see section 4.5).

Sudden withdrawal of prolonged treatment with Abbonate should be avoided as this may lead to withdrawal symptoms such as anxiety, restlessness, insomnia, drowsiness, or delirium (see section

4.2). Treatment should therefore be discontinued by slow reduction in dose over a period of at least two weeks.

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 Appendix V.

4.9 Overdose

Tranylcypromine is characterized by a significant acute toxicity with risk for a poisoning which is difficult to treat. The emergency unit should be contacted immediately at a suspected overdose. Careful monitoring of blood pressure is necessary. The patient should be carfully monitored for at least one week after the overdose, since symtoms of overdose may be delayed or be prolonged. The possibility of involvement of several medicinal products should be considered.

Symptoms of overdose
Life-threatening symptoms of overdose with tranylcypromine affect the central nervous system (confusion, hyperexcitation including epileptic seizures, unconsciousness to coma, fever, hyperthermia), respiratory function (including respiratory arrest) and the cardiovascular system (severe blood pressure fluctuations, conduction abnormalities) and the muscles (severe muscle spasms).

Treatment of overdose
In addition to careful monitoring of pulse, blood pressure, respiration and temperature, resources for controlled ventilation must be available.

Due to the rapid absorption of tranylcypromine, measures to prevent absorption (gastric lavage if used should only be performed by individuals with proper training and expertise, administration of activated charcoal) are only useful if treatment can be initiated shortly after overdose intake. Hemodialysis and hemoperfusion are indicated only within the first hours after overdose intake and even then, are of uncertain value. Although the acidification of urine (e.g. by administration of ammonium chloride) leads to an increased excretion of tranylcypromine, it should be noted that this measure only has a limited effect because the irreversible inhibition of monoamine oxidase by tranylcypromine is not eliminated. The effects of overdose should be treated symptomatic until the novo synthesis of monoamine oxidase is restored.

Symptom control of intoxication
Careful monitoring of blood pressure after overdose is absolutely necessary. The patient should be carefully monitored for at least one week after intake of the overdose, as the symptoms of an overdose may be delayed or may be prolonged.

In hypertensive crisis (acute blood pressure elevation above 180/100 mm Hg) antihypertensives such as nifedipine are indicated. For severe hypertension, intravenous phentolamine or nitroprusside can be administered.

Severe hypotension should preferably be treated with intravenous fluids. If the response to intravenous fluids is insufficient, norepinephrine (continuous infusion) may be administered.

In case of severe agitation and/or pronounced skeletal muscle rigidity, treatment with benzodiazepines is recommended. In severe muscle cramps, muscle relaxation with non-depolarizing muscle relaxants (pancuronium, vecuronium) and ventilation may be necessary. In ventricular tachyarrhythmia, lidocaine, procainamide, or phenytoin may be considered. Diazepam is recommended for convulsions.

Treatment of serotonin syndrome
If possible, but only when available as an oral form of administration, cyproheptadine can be used in serotonin syndrome with 5-HT blockage.

Chlorpromazine may also be used in serotonin syndrome with 5-HT blockage and agitated states, but the risk of lowering of the seizure threshold, inhibition of sweating, hypotension and dystonia should be considered.

For hyperpyrexia, treatment as described in section Symptom control of intoxication is necessary. The treatment of severe serotonin syndrome due to interactions with serotonergic medicinal products corresponds to the treatment proposed in serotonin syndrome due to tranylcypromine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics. Antidepressants, monoamine oxidase inhibitors, non-selective. ATC code: N06AF04

Tranylcypromine belongs to the group of non-selective and irreversible non-hydrazine monoamine oxidase (MAO) inhibitors. It has a fast acting (within 2–8 days) strong stimulating and psychomotor activating effect, while the mood and antidepressant effect develops slowly (about 3–5 weeks).

The mechanism of antidepressant action is not fully understood. Within two hours after administration of non-selective inhibition of MAO-A and-B, the intracellular and intraneural inactivation of biogenic amines such as serotonin, noradrenalin and dopamine is prevented. Resulting in a larger availability of neurotransmitters in the CNS. Although tranylcypromine and its metabolites are excreted completely within 24 hours after the last dose, it takes 3 to 5 days to restore full activity of the enzyme monoamine oxidase because of the irreversible MAO inhibition.

In the long term, tranylcypromine reduces the density of β-adrenoceptors and serotonergic 5-HT_2 receptors.

Tranylcypromine is a racemate of (-)- and (+)-isomers: the (+)-isomer has a greater inhibitory effect on monoamine oxidase, the (-)-isomer can also inhibit noradrenaline reuptake.

5.2 Pharmacokinetic properties

Absorption
Tranylcypromine is rapidly absorbed after oral administration. Maximum plasma levels are expected 0.5–3.5 h after the use of oral dosage forms. For patients using tranylcypromine chronically, an average maximum plasma level of 112 ng/ml is measured 2 hours after a single dose of 20 mg of tranylcypromine.

Distribution
The volume of distribution is 1.1 to 5.7 l/kg of body weight. It is not known if tranylcypromine is excreted in human breast milk. Evidence on the impact of the foetal circulation is not known.

Biotransformation
Primary hepatic biotransformation products are p-hydroxy tranylcypromine and N-acetyl tranylcypromine. Only about 4% of the dose is excreted in the urine as unchanged tranylcypromine. Even after administration of high doses of tranylcypromine, amphetamine was not identified as a metabolite in urine or plasma in humans.

Elimination
A half-life of approximately 2.5 hours was found in a study in patients with a depression after a single dose of 20 mg of tranylcypromine. Excretion is mostly in the form of metabolites (hippuric acid and benzoic acid) into the bile and mainly via the kidney. The renal excretion of tranylcypromine is strongly dependent on pH; low pH values promote the excretion.

Stereoselectivity
The plasma concentration of the (-)-isomer is always higher than that of the (+)-isomers. Maximum blood levels are usually reached 0.5–3.5 hours after administration.

5.3 Preclinical safety data

Limited data from in-vitro studies does not reveal mutagenic properties of tranylcypromine. Animal sutides are incomplete in regards to reproduction toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline
Calcium hydrogen phosphate (anhydrous)
Pregelatinised starch
Silica colloidal, anhydrous
Talc

Tablet shell
Polyvinyl alcohol, partially hydrolysed
Macrogol
Ponceau 4 R (E 124)
Talc
Titanium dioxide (E 171)
Indigo carmine aluminium lake (E 132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-PVC/PVdC blister: 30, 60, 90 and 105 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

2024-04-04