

Tofranil® 25mg
(Imipramine Hydrochloride)
Tablets USP

Composition:

Each sugar coated tablet contains:

Imipramine hydrochloride ... 25mg.

Finished Product Specs.: USP.

Therapeutic / pharmacological class

Tricyclic antidepressant, noradrenaline/serotonin reuptake inhibitor.

Composition of product

N-(γ - Dimethylaminopropyl)-iminodibenzyl hydrochloride.

(=imipramine hydrochloride).

Dosage forms

Sugar coated tablets of 25mg, imipramine hydrochloride.

Properties

Pharmacodynamics

Characteristic of imipramine is a multivalent pharmacological spectrum of action, which includes alpha-adrenolytic, anti-histaminic, anti-cholinergic, and 5-HT-receptor blocking properties. However, the therapeutic activity of imipramine is believed to be based above all on its ability to inhibit the neuronal reuptake of noradrenaline (NA) and serotonin (5-HT).

Imipramine belongs to the category of so-called "mixed" reuptake blockers, i.e., it inhibits the reuptake of NA and 5-HT to approximately the same extent.

Pharmacokinetics

Absorption

Imipramine is absorbed quickly and completely following oral administration. The intake of food has no effect on its absorption and bioavailability. During, its first passage through the liver, orally administered imipramine becomes partly converted to desmethylimipramine, a metabolite which likewise exhibits antidepressive activity. Consequently, following parenteral administration the initial concentration of this metabolite is lower.

Plasma concentration

During oral administration of 50mg 3 times daily for 10 days, the mean steady-state plasma concentrations of imipramine and desmethylimipramine were 33-85 ng/ml and 43-109 ng/ml respectively. Owing to lower clearance in the plasma, resulting in increased systemic availability, elderly patients require lower doses of imipramine than patients in intermediate age groups. In patients with severe renal damage, no change occurs in the renal excretion kinetics of the active substances as compared with healthy subjects.

Protein binding: mean 86%

Distribution volume: mean 21 l/kg.

Plasma half-life: mean approx 20 hours.

Excretion:

Approx 80% is excreted in the urine and approx 20% in the faeces, chiefly in the form of inactive metabolites.

Therapeutic Information

Indications

Depressive states of varying aetiology and symptomatology, including masked forms:

- Endogenous depression (unipolar, bipolar, involutional depression).
- Somatogenic depression (organic, symptomatic).
- Psychogenic depression (neurotic, reactive and exhaustion depression,

depression associated with personality disorders).

- Depressive mood disorders of a reactive, neurotic or psychopathic nature including their somatic equivalents, also in children.

- Depressive syndromes in the presenium and senium, associated possibly with hypochondriasis, as well as compulsive weeping and lack of emotional control.

- Depressive syndromes due to arteriosclerosis, cerebrovascular accidents, Parkinson's disease, chronic somatic diseases, chronic painful conditions and alcoholism.

- Further indications: panic attacks, pavor nocturnus, nocturna enuresis (from the age of 5 years onward and provided the possibility of organic causes has first been excluded), chronic painful conditions.

Contra-indications

Known hypersensitivity to tricyclic antidepressants of the dibenzazepine group.

Tofranil must not be given in the acute stage of myocardial infraction.

Adverse reactions

Anticholinergic effects

Frequently dryness of the mouth, constipation, sweating, hotflushes, disorders of visual accommodation, and blurred vision. Occasionally disturbances of micturition, isolated cases of mydriasis, glaucoma and paralytic ileus.

Central nervous system

Psychic effects

Occasionally fatigue, drowsiness, sleep disturbances, increased anxiety, feelings of unrest and agitation, swings from depression to hypomania or mania, symptoms of delirium such as confusion accompanied by disorientation and hallucinations (particularly in geriatric patients and those suffering from Parkinson's disease).

Neurological effects

Frequently fine tremor. Occasionally paraesthesiae (numbness, tingling sensation, symptoms suggestive of peripheral neuropathy), headache, dizziness. Rarely epileptic seizures.

Cardiovascular system

Frequently sinus tachycardia and clinically irrelevant ECG Changes (T and ST changes) in patients of normal cardiac status, postural hypotension.

Respiratory tract

Isolated cases of allergic alveolitis (pneumonia) with or without eosinophilia.

Gastro-intestinal tract

Occasionally nausea, vomiting, anorexia. Rarely elevated transaminases.

Skin

Occasionally allergic skin reactions (skin rash, urticaria). Isolated cases of pruritus.

Endocrine system and metabolism

Frequently weight gain. Occasionally disturbances of libido and potency. Isolated cases of enlarged mammary glands, galactorrhoea, SIADH (syndrome of Inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar, weight loss.

Blood

Isolated cases of eosinophilia, leucopenia, agranulocytosis, purpura and thrombocytopenia.

Miscellaneous

Although not indicative of addiction, occasionally withdrawal symptoms following abrupt discontinuation of treatment nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness and anxiety. Isolated cases of tinnitus, drug fever.

Warnings

Combined treatment with Tofranil and an MAO inhibitor should, wherever possible, be avoided. It should be employed only in selected patients suffering from

refractory depression and only in a hospital setting. In all such cases treatment with Tofranil, in an individually adapted dosage, should be started before- or at least simultaneously with the MAO inhibitor, in order to avoid potentially serious interactions, such as hyperactivity, hypertensive crises, hyperperyrexia, spasticity, convulsions, coma.

Caution is called for when employing Tofranil in:

- Patients with cardiovascular insufficiency, atrioventricular block (grades I to III) and arrhythmias.

- Patients with narrow-angle glaucoma.

- Patients with disorders of micturition due to an impeded flow of urine (e.g. in diseases of the prostate).

- Patients with a low convulsion threshold (e.g. due to brain damage of varying aetiology, epilepsy, alcoholism).

- Patients with severe hepatic or renal diseases.

- Patients with tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), in whom the drug may provoke hypertensive crises.

Concomitant treatment with Tofranil and electroconvulsive therapy should only be resorted to under careful supervision.

Many patients with panic disorder experience intensified anxiety symptoms at the start of the treatment with antidepressants: This paradoxical initial increase in anxiety is most pronounced during the first few days of treatment and generally subsides within two weeks.

Precautions

Tofranil should be employed with caution in patients with cardiovascular disorders, especially those who have a history of conduction disorders (see "Warnings"); as well as in elderly patients. Monitoring of cardiovascular function and ECG is called for in such cases. In order to guard against possible cardiotoxic effects, a daily dosage of 2.5mg/kg should not be exceeded in children.

Before initiating treatment it is advisable to check the patient's blood pressure, because individuals with hypotension or a labile circulation may react to the drug with a fall in blood pressure.

Caution is indicated in patients with or in the case of concomitant treatment with thyroid preparations.

The blood count should also be monitored during treatment with Tofranil (especially if the patient develops fever, sore, throat or other symptoms such as are associated with influenzal infections).

It is also advisable to monitor hepatic and renal function during long term therapy with Tofranil.

Owing to its activating effect, Tofranil may cause anxiety, feelings of unrest, and hyperexcitation in agitated patients and patients with accompanying schizophrenic symptoms.

A swing from depression to hypomania or mania is possible in patients with bipolar effective disorders.

If there is a risk of suicide, the patient should be kept under very careful surveillance during treatment with Tofranil. In these cases initial combined therapy with sedative neuroleptic agents and/or benzodiazepines has yielded good results. Before surgical interventions, the anaesthetist should be notified that the patient has been receiving Tofranil, since little is known about interactions between concomitantly administered tricyclic antidepressants and anaesthetics.

Mutagenicity, carcinogenicity and reproduction toxicity studies

Imipramine has no mutagenic or carcinogenic potential. Studies in four species (mouse, rat, rabbit and monkey) led to the conclusion that orally administered, Tofranil

has no teratogenic potential, Experiments with high doses of parenterally administered Tofranil, which are described in the literature, resulted mainly in severe maternal and embryotoxic effects; they were thus inconclusive with regard to teratogenic effects.

Use during pregnancy and lactation

Experience with Tofranil in pregnancy is limited. Since there have been isolated reports of a possible connection between the use of Tofranil and adverse effects on the foetus, treatment with Tofranil should be avoided during pregnancy. The active substance of Tofranil and its metabolite desmethylimipramine pass into the breast milk in small quantities. Since nothing is known about the clinical relevance of this finding as regards the infant, babies should be weaned or the medication withdrawn.

Effects on ability to drive or use machines

Tofranil occasionally causes fatigue and, in rare instances, other central nervous symptoms which may impair the patient's reactions.

Interactions with other medicaments and other forms of interaction
If Tofranil is to be employed following treatment with an MAO inhibitor, it is absolutely essential that an interval of at least 14 days should elapse before-starting therapy, because otherwise severe interactions may occur.

The same precaution should be taken when administering a MAO inhibitor after previous treatment with Tofranil. In either instance, medication with Tofranil or with the MAO inhibitor should be initiated cautiously and the dosage slowly raised stepwise until the patient is optimally stabilised.

The cardiovascular effects of sympathomimetics, such as adrenaline, noradrenaline and amphetamine (as well as of nasal drops and local anaesthetics containing sympathomimetics) may be potentiated by tricyclic antidepressants. Tricyclic antidepressants may also increase the effect of alcohol and central depressants. drugs (e.g. barbiturates; benzodiazepines, or general anaesthetics), as well as that of anticholinergic agents (e.g. atropine, biperiden, levodopa). Tricyclic antidepressants should not be employed in combination with anti-arrhythmic agents of the quinidine type.

Substances which activate the hepatic mono-oxygenase enzyme system (e.g. barbiturates, phenytoin, nicotine) may lower the plasma concentration of tricyclic antidepressants and so reduce their antidepressive effect.

In addition, concomitant administration of imipramine and phenytoin may lead to elevated serum phenytoin concentrations.

Neuroleptic agents (e.g. phenothiazines) may increase the plasma concentration of imipramine. No such effects are known to occur in combination with diazepam. Since cimetidine raises the plasma concentration of imipramine, the dosage of imipramine should be reduced.

Methylphenidate may cause the plasma concentration of tricyclics to rise and so intensify their antidepressive effect.

If administered concomitantly with oestrogens, the dose of imipramine should be reduced.

Dosage and method of administration

The dosage and mode of administration should be determined individually and adapted to the patient's condition.

In principle, every effort must be made to achieve an optimum effect while keeping the doses as low as possible and increasing the dosage cautiously, particularly when treating elderly patients or adolescents.

Depression and depressive syndromes

Oral treatment on an ambulant basis

Initiate treatment with 25mg 1-3 times daily. Raise the daily dosage stepwise to 150-200mg. This dosage should be reached by the end of the first week and adhered

ٹوفرانل

برایات برائے مریض:

ٹوفرانل صرف ڈاکٹر کی ہدایت پر ہی استعمال کریں۔

برائے مہربانی خوراک کے بارے میں ڈاکٹر کی دی ہوئی ہدایات پر سختی سے عمل کریں۔
ٹوفرانل سے علاج لمبے عرصے تک کیا جاتا ہے۔ علاج کی مدت صرف ڈاکٹر ہی متعین کر سکتا ہے۔

علاج کو ڈاکٹر کی ہدایت کے بغیر نہ تو ایک دم بدلیں اور نہ ہی روکیں۔

احتیاط

اگر آپ مندرجہ ذیل امراض میں سے کسی میں بھی مبتلا ہوں تو اپنے ڈاکٹر کو بتائیں کیونکہ بعض صورتوں

میں ٹوفرانل کا استعمال نہیں کرنا چاہئے۔

اگر آپ دل کے کسی عارضہ میں مبتلا ہوں یا آپ کے دل کی دھڑکن غیر متوازن ہے۔ یا آپ کو پچھلے ۸ ہفتوں

میں دل کا دورہ پڑا ہو۔

● اگر آپ آنکھوں میں دباؤ کا شکار ہوں۔

● اگر آپ پیشاب کے رُکنے کی شکایت میں مبتلا ہوں۔ (Enlarged prostate)

● اگر آپ جگراور گردے کی شدید بیماری میں مبتلا ہوں۔

● اگر آپ کو مرگی یا کسی بھی قسم کے دورے پڑتے ہوں۔

● اگر آپ دواؤں سے الہربک ہوں۔

● اگر آپ حاملہ ہیں یا حاملہ ہونے والی ہوں یا بچے کو اپنا دودھ پلاتی ہیں تو اپنے ڈاکٹر کو اس بات سے

آگاہ کریں۔

دوائیں فائدے دینے کے علاوہ اکثر غیر ضروری اثرات بھی پیدا کر سکتی ہیں۔ گوکہ یہ غیر ضروری اثرات

ہر مریض میں نہیں ہوتے اور عموماً علاج کے شروع ہونے کے چند دنوں بعد ختم ہو جاتے ہیں۔

ٹوفرانل سے علاج کے شروع میں ہوسکتا ہے کہ آپ کو مندرجہ ذیل شکایات پیدا ہوں۔

منہ کا خشک ہونا، پسینہ آنا، آنکھوں میں دھندلا پن، تھکاوٹ، بے آرمی، سر میں درد، چکر آنا،

دل کا تیز دھڑکنا، متلی اور قبض۔

اگر آپ کسی بھی قسم کی کوئی اور دوا استعمال کر رہے ہوں تو اپنے ڈاکٹر کو اس کی تفصیل سے آگاہ کریں۔

30°C سے کم درجہ حرارت پر رکھیں۔

گرمی، روشنی اور نمی سے محفوظ رکھیں۔

تمام دواؤں بچوں کی پہنچ سے دور رکھیں۔

convulsions, speech disorders or feverish, influenza-like symptoms or if any of the unwanted effects mentioned previously persist for a long time. You should also inform your doctor if you have an overactive thyroid, if problems occur with your teeth or if you are due to undergo surgery (including minor operations such as the removal of a finger nail).

At the start of treatment for panic attacks, Tofranil may increase your feelings of anxiety. This is transient and generally subsides within 2 weeks. Give your doctor exact details of any other medication you are receiving (including eye or nose drops).

It is also important that, during treatment with Tofranil, you should discuss with your doctor any problems you may have, as well as your frame of mind (e.g. severe dejection or sadness, but also increased energy or out breaks of anger).

Dosage / Use

Tofranil should only be taken *if prescribed by a doctor*: Please follow your doctor's instructions exactly regarding the dosage. Depressive states and panic attacks require lengthy treatment with Tofranil, the duration of which must be determined by your doctor. Do not change or interrupt the treatment without the doctor's approval.

Safety not concerning children

All drugs should be kept out of the reach of children.

Pharmaceutical information

Pharmaceutical incompatibilities

Incompatibility none known to date

Storage conditions

Store below 30°C.

Protect from heat, light and moisture.

Nature and contents of containers

200 sugar coated tablets of Tofranil 25mg.

Safety note concerning children

Keep all medicines out of the reach of children.

INFORMATION FOR THE PATIENTS

Properties / Scope of use

Tofranil is mainly used to treat various forms of depression. It can also be used in panic attacks (recurrent attacks of anxiety), chronic painful conditions and bed-wetting.

Restrictions on use

In certain circumstances you must not take Tofranil, or may only do so subject to a through medical examination.

For this reason you should inform your doctor if you are suffering from any of the following conditions:

- Muscular weakness of the heart
- Irregular heart beat
- Heart attack within the previous 8 weeks
- Raised pressure within the eye
- Impeded flow of urine (e.g. diseases of the prostate)
- Severe liver or kidney disease
- Proneness to convulsions
- Allergic reactions to medicines

Pregnancy and lactation

You should also inform your doctor if you are pregnant, expect to become pregnant, or are breast-feeding.

Unwanted effects / Precautions

Medicines may produce unwanted effects in addition to their desirable therapeutic effects. However, these unwanted effects do not occur in every case and they often disappear after the first few days of treatment. Particularly at the beginning of treatment, you may suffer from dryness of the mouth, sweating, blurred vision, fatigue, feelings of unrest, dizziness, headache, palpitations, nausea or constipation. Other unwanted effects may also occur, such as muscular pain, trembling, confusion, a racing pulse, sleep disturbances, increase in weight and very rarely a decrease in weight and loss of hair.

You should consult your doctor if you experience an irregular heart beat, jaundice, skin rash, itching, swelling of the breasts and discharge of milk, delusions,

Treatment

There is no specific antidote. The use of physostigmine is controversial, since it may increase the risk of epileptic seizures.

Where the drug has been taken by mouth, try to induce vomiting; otherwise the stomach must be irrigated. Activated charcoal should be administered; In all patients with ECG abnormalities, cardiac function should-even after the ECG tracings have reverted to normal-be kept under close observation for at least another 72 hours, because relapses may occur.

- The following measures should be taken in cases of overdosage:
- In respiratory failure intubation and artificial respiration.
 - In severe hypotension: the patients should be placed in an appropriate position and be given a plasma expander, dopamine or dobutamine by intravenous drip.
 - Cardiac arrhythmias must be treated according to the requirements of the case.
 - Implantation of a cardiac pacemaker should be considered.
 - Low potassium values and acidosis should be corrected.
 - In convulsions: diazepam should be given i.v. or another anti-convulsant such as phenosobarbitone or paraldehyde (these substances may exacerbate existing respiratory failure, hypotension or coma).
 - Dialysis and haemodialysis are of no use.

to until a clear-cut improvement has occurred. The subsequent maintenance dose, which must be individually determined by cautiously reducing the dosage, usually amounts to 50-100mg daily.

Treatment in hospital with coated tablets

Initiate treatment with 25mg t.i.d. Raise the daily dosage stepwise by 25mg, until a dose of 200mg has been reached, and adhere to this dose until the depressive condition has improved. In severe cases the dose may be increased to 100mg t.i.d. Once a distinct improvement has set in the subsequent daily maintenance dose should be determined according to the patient's individual requirements (generally 100mg).

Panic attacks: Initially 1 tablet of 25mg daily, possibly in combination with a benzodiazepine (see "Warnings"). Depending on how the medication is tolerated; raise the dosage until the desired response is obtained, while at the same time gradually withdrawing the benzodiazepine. The daily dosage required varies greatly from patient to patient and lies between 75 and 150mg. If necessary it can be increased to 200mg. It is recommended that the treatment should not be discontinued before 6 months have elapsed and that during this time the maintenance dose should be slowly reduced.

Chronic painful conditions: The dosage must be individualised (25-300mg daily). A daily dosage of 25-75mg is generally sufficient.

Geriatrics:

Initiate treatment with 1 tablet of 25mg daily. Gradually raise the dosage to an optimum level of 25-50mg daily, which should be reached after about 10 days and then adhered to until the end of treatment.

Paediatrics:

Initiate treatment with 1 tablet of 25mg daily. Over a period of 10 days increase the daily dosage to 2 tablets in children aged 5-8, to 25-50mg in those aged 9-14 and to 50-75mg in patients aged over 14 years.

Nocturnal enuresis (only in children aged 5 years or older): Initial daily dose in children aged 5-8 years: 1 tablet of 25mg; in children aged 9-12: 1-2 tablets of 25mg; in older children: 1-3 tablets of 25mg. The higher doses apply to those cases which do not respond fully to treatment within one week. The tablets should be given in a single dose after the evening meal, although children who wet their beds early in the night should be given part of the dose beforehand (at 4 pm). Once the desired response has been achieved the treatment should be continued (for 1-3 months), reducing the dose, stepwise to the maintenance dose.

Overdosage

Since children react much more sensitively than adults to acute overdosages of tricydics and since fatalities have been reported, every effort should be made to avoid an overdosage (see "Safety note concerning children"), which, if it does occur, should be treated with extreme care.

Signs and symptoms

The first signs and symptoms of poisoning with tricyclic antidepressants generally take the form of severe anticholinergic reactions, which set in about 1/2-2 hours after the drug has been taken.

The following signs and symptoms may be encountered: Central nervous system: drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes muscular rigidity, athetoid and choreiform movements, convulsions.

Heart: arrhythmia, tachycardia, conduction disorders, heart failure; in very rare cases, cardiac arrest.

In addition, respiratory depression, cyanosis, hypotension, shock, vomiting, fever, mydriasis, sweating and oliguria or anuria may occur.



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