Tofranil®

NOVARTIS

Tricyclic antidepressant
Noradrenaline / serotonin re-uptake blocker

COMPOSITION

Tofranil 10 mg sugar-coated tablets: imipramine hydrochloride 10 mg, tableting and coating excipients.

Tofranil 25 mg sugar-coated tablets: imipramine hydrochloride 25 mg, tableting and coating excipients.

PROPERTIES / ACTIONS

Imipramine has several pharmacological properties, including alpha-adrenolytic, antihistaminic, anticholinergic and 5-HT-receptor-blocking properties. However, its therapeutic activity is probably due primarily to the inhibition of neuronal noradrenaline (NA) and serotonin (5-HT) re-uptake.

Imipramine is a "mixed" re-uptake blocker, i.e. it inhibits the re-uptake of NA and 5-HT to about the same extent.

PHARMACOKINETICS

Absorption

Imipramine is absorbed rapidly and almost completely from the gastrointestinal tract. Food has no effect on its absorption and bioavailability.

During first passage through the liver, orally administered imipramine is partially converted to desmethylimipramine, a metabolite which also exhibits antidepressant activity.

Following oral administration of 50 mg t.i.d. for 10 days, mean steady-state plasma concentrations of imipramine and desmethylimipramine were 33–85 ng/mL and 43–109 ng/mL, respectively.

Distribution

About 86% of imipramine binds to plasma proteins. Concentrations of imipramine in the cerebrospinal fluid and the plasma are highly correlated.

The apparent distribution volume is about 21 L/kg bodyweight.

Imipramine and its metabolite desmethylimipramine are both excreted in breast milk in concentrations similar to those found in the plasma.

Metabolism

Imipramine is extensively metabolized in the liver. It is eliminated mainly by demethylation, and to a lesser extent by hydroxylation. Both metabolic pathways are under genetic control.

Elimination

Imipramine is eliminated from the blood with a half-life of approx. 19 hours.

About 80% is excreted in the urine and about 20% in the faeces, mainly in the form of inactive metabolites. Urinary excretion of unchanged imipramine and of the active metabolite desmethylimipramine is about 5% and 6%, respectively. Only small quantities are excreted in the faeces.

Pharmacokinetics in special clinical situations

Plasma concentrations of imipramine are higher in elderly than in younger patients owing to reduced metabolic clearance.

In children mean clearance and elimination half-life do not differ significantly from those in adults, but interindividual variability is high.

Renal excretion of imipramine and its biologically active unconjugated metabolites are not altered in patients with severe renal impairment. However, steady-state plasma concentrations of the conjugated metabolites, which are thought to be biologically inactive, are elevated. The clinical significance of this finding is not known.

INDICATIONS / POTENTIAL USES

Depression of various aetiologies, including endogenous, organic and psychogenic, and depression associated with personality disorders or chronic alcoholism.

Additional uses: Panic attacks, night-terrors (pavor nocturnus), nocturnal enuresis (only in patients aged 6 years or older and after exclusion of organic causes), chronic painful conditions (in particular pain associated with cancer, neuropathic pain and idiopathic pain syndrome).

DOSAGE / ADMINISTRATION

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

The aim is to achieve an optimum effect while keeping doses as low as possible and increasing them cautiously, particularly in elderly patients and adolescents, who generally show greater response to Tofranil than patients in the intervening age groups.

Depression and depressive syndromes

Ambulatory care

Start treatment with 25 mg 1–3 times daily. Raise the daily dosage gradually to 150–200 mg daily. This dosage should be reached by the end of the first week and maintained until a clear improvement is seen. The maintenance dose, which must be individually determined by cautiously reducing the dosage, is usually 50–100 mg daily.

Hospital care

Start treatment with 25 mg 3 times daily. Raise the dosage by 25 mg daily until a dose of 200 mg has been reached, and keep to this dose until the patient's condition has improved. In severe cases the dose may be increased to 100 mg three times daily. Once a clear improvement has been achieved, the maintenance dose should be determined according to the patient's individual requirements (generally 100 mg daily).

Lower doses should be used in an ambulatory-care than in a hospital setting with its closer patient supervision.

Panic attacks

Initially one tablet of 10 mg Tofranil daily, possibly in combination with a benzodiazepine (see ***Precautions***). Depending on how the medication is tolerated, raise the dosage until the desired response is obtained, while gradually withdrawing the benzodiazepine. The daily dosage required varies greatly from patient to patient, between 75 mg and 150 mg. If necessary, it can be raised to 200 mg. Withdrawal is best effected over a period of at least six months by progressive reduction of the maintenance dose.

Chronic painful conditions

The dosage must be individualized (25–300 mg daily). A daily dose of 25–75 mg is generally sufficient.

Elderly patients

Start treatment with one tablet of 10 mg Tofranil daily. Gradually increase the dosage to 30–50 mg daily (optimum level) over a period of about 10 days, then maintain until the end of treatment.

Children

Night-terrors (pavor nocturnus)

Start treatment with one tablet of 10 mg daily, then increase the daily dosage over a period of 10 days to 2 tablets in children aged 5–8 years, 20–50 mg in those aged 9–14 years, and 50–80 mg in patients aged over 14 years. In order to guard against possible cardiotoxic effects in children, a daily dosage of 2.5 mg/kg should not be exceeded.

Nocturnal enuresis

(only in children aged 6 years or older)

Initial daily dose in children aged 6–8 years: 2–3 tablets of 10 mg; in children aged 9–12 years: 1–2 tablets of 25 mg; in older children: 1–3 tablets of 25 mg. The higher doses are for patients who do not respond fully to treatment within one week. The daily dose should not exceed 2.5 mg/kg. Treatment should be given for a maximum of three months, inclusive of the period of gradual withdrawal.

The tablets should be given in a single dose after the evening meal, but children who wet the bed early in the night should be given part of the dose earlier (at 16:00).

No experience is available in children under 6 years of age.

RESTRICTIONS ON USE

Contraindications

Hypersensitivity to imipramine or any of the excipients, or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group.

Tofranil should not be given in combination with, or within 14 days before or after a MAO inhibitor (see **INTERACTIONS**). Concomitant use of selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated.

Recent myocardial infarction.

Precautions

Cardiovascular disorders

Particular caution is called for in patients with cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders (e.g. grade I–III atrioventricular block), or arrhythmias. Monitoring of cardiac function and the ECG is indicated in such patients, as well as in elderly patients.

Before starting treatment it is advisable to check the patient's blood pressure because of the possibility of a reduction in patients with hypotension or circulatory instability.

Central nervous system

Tricyclic antidepressants are known to lower the convulsion threshold and Tofranil should therefore be used with extreme caution in patients with epilepsy or other predisposing factors (e.g. brain damage due to various causes, concomitant use of neuroleptics, withdrawal of alcohol or drugs with anticonvulsant properties such as benzodiazepines). The occurrence of seizures seems to be dose-dependent. The recommended total daily dose should therefore not be exceeded.

Tofranil should be given in conjunction with electroconvulsive therapy only under close supervision.

Many patients with panic disorder experience more marked anxiety at the start of 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.

Activation of psychosis has occasionally been observed in schizophrenic patients receiving tricyclic antidepressants.

As a result, Tofranil may cause increased anxiety, restlessness and excitation in patients with agitation or concomitant schizophrenic symptoms.

In predisposed and elderly patients, Tofranil may provoke anticholinergic (delirious) psychosis, particularly at night. These disappear without specific treatment within a few days of withdrawing the drug.

Hypomanic or manic episodes have also been reported during a depressive phase in patients with bipolar affective disorders receiving treatment with a tricyclic antidepressant. In such cases it may be necessary to reduce the dosage of Tofranil or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with Tofranil may be resumed if required.

Risk of suicide is inherent to severe depression and may persist until significant remission occurs. At the beginning of treatment, combined therapy with benzodiazepines or neuroleptics may be indicated (see **INTERACTIONS**).

Blood

Although changes in the white blood cell count have been reported with Tofranil only in isolated cases, periodic blood cell counts and monitoring for symptoms such as fever and sore throat are called for, particularly during the first few months of therapy and during prolonged treatment. Tofranil must be withdrawn if the neutrophil count falls to a pathological level.

Endocrine system

Caution is indicated in patients with hyperthyroidism and patients receiving thyroid preparations, since the anticholinergic action of Tofranil is likely to increase the overall risk of unwanted cardiac effects.

Liver/kidneys

Periodic monitoring of liver enzyme levels is recommended in patients with liver disease.

Caution is called for when giving tricyclic antidepressants to patients with severe hepatic or renal disease, or tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma) because of the risk of precipitating hypertensive crisis.

Gastrointestinal tract

Caution is called for in patients with chronic constipation. Tricyclic antidepressants may cause paralytic ileus, particularly in elderly and bedridden patients.

Other

Because of its anticholinergic properties, Tofranil should be used with caution in patients with a history of increased intraocular pressure, narrow angle glaucoma, or urinary retention (e.g. due to prostate disease).

Decreased lacrimation and accumulation of mucoid secretions due to the anticholinergic properties of tricyclic antidepressants may cause damage to the corneal epithelium in patients with contact lenses.

Tofranil should be withdrawn as early as possible prior to general or local anaesthesia (see **INTERACTIONS**). (The anaesthetist must be informed that the patient is receiving treatment with Tofranil.)

An increase in dental caries has been reported during long-term treatment with tricyclic antidepressants. Regular dental check-ups are therefore advisable during long-term treatment.

Patients receiving Tofranil should not expose themselves to intense sunlight as there have been reports of photosensitization.

Abrupt withdrawal should be avoided because of possible adverse reactions (see **ADVERSE REACTIONS**).

Effects on vigilance/reactions

Patients receiving Tofranil should be warned that blurred vision, drowsiness and other CNS symptoms (see **ADVERSE REACTIONS**) may occur, in which case they should not drive, use machines or do anything else requiring complete alertness. Patients

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should also be warned that alcohol and other drugs may potentiate these effects (see **INTERACTIONS**).

Pregnancy and lactation
Animal studies have revealed no adverse effects on the foetus. There is definite evidence of risk to the human foetus, but this may be outweighed by the therapeutic benefit for the mother. Experience with Tofranil in pregnant women 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 and should only be considered if absolutely essential and if there is no alternative lower-risk drug.

Infants born to mothers treated with Tofranil during pregnancy showed symptoms such as respiratory disorders, lethargy, colic, irritability, hypotension, hypertension, trembling and convulsions over the first few hours or days of life. To avoid such symptoms, Tofranil should be withdrawn at least seven weeks before the estimated date of delivery, if medically justified.

Small quantities of the active ingredient of Tofranil and its metabolite desmethylimipramine are excreted in breast milk. The clinical relevance of this is not known, and mothers should therefore stop breastfeeding or discontinue Tofranil treatment.

ADVERSE REACTIONS
Adverse reactions are usually transient, disappearing as treatment continues or as a result of dose reduction. They do not always correlate with plasma drug levels or dose. It is often difficult to distinguish certain adverse reactions from symptoms of depression such as fatigue, sleep disturbances, agitation, anxiety, constipation and dry mouth.

If severe neurological or mental reactions occur, Tofranil should be withdrawn.

Elderly patients are particularly susceptible to anticholinergic, neurological, mental and cardiovascular effects. Their ability to metabolize and eliminate drugs may be reduced, leading to a risk of elevated plasma levels at therapeutic doses.

Anticholinergic effects
Common: Dry mouth, constipation, sweating, hot flushes, disorders of visual accommodation, blurred vision.

Occasional: Disturbances of micturition.

Isolated cases: Mydriasis, glaucoma.

Central nervous system
Mental effects
Occasional: Drowsiness, fatigue, restlessness, confusion, delirium, disorientation, hallucinations (particularly in elderly patients and patients with Parkinson's disease), increased anxiety, agitation, sleep disturbances, swing from depression to hypomania or mania.

Rare: activation of psychotic symptoms.

Isolated cases: Aggressiveness.

Neurological effects
Common: Fine tremor.

Occasional: Paraesthesia, headache, dizziness.

Rare: Epileptic seizures.

Isolated cases: EEG changes, myoclonus, weakness, extrapyramidal symptoms (including tardive dyskinesia), ataxia, speech disorders, drug fever.

Cardiovascular system
Common: Sinus tachycardia and clinically irrelevant ECG changes (e.g. T and ST changes) in patients with normal cardiac status, orthostatic hypotension.

Occasional: Arrhythmias, conduction disorders (broad QRS and PR complex, bundle-branch block), palpitations.

Isolated cases: Increased blood pressure, cardiac decompensation, peripheral vasospastic reactions.

Gastrointestinal tract
Occasional: Nausea, vomiting, loss of appetite, diarrhoea.

Isolated cases: Stomatitis, changes involving the tongue, abdominal disorders.

Liver
Occasional: Elevated transaminases.

Isolated cases: Hepatitis with or without jaundice.

Skin
Occasional: Allergic skin reactions (rash, urticaria).

Isolated cases: Pruritus, petechiae, photosensitivity, oedema (local or generalized), hair loss.

Endocrine system and metabolism
Common: Weight gain.

Occasional: Disturbances of libido and potency.

Isolated cases: Breast enlargement, galactorrhoea, SIADH (syndrome of inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar, weight loss.

Hypersensitivity reactions
Isolated cases: Allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension.

Sensory organs
Isolated cases: Tinnitus.

Blood
Isolated cases: Eosinophilia, leucopenia, agranulocytosis, purpura and thrombocytopenia.

Others
The following occasionally occur after abrupt withdrawal or dose reduction: Nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, anxiety.

INTERACTIONS
MAO inhibitors
An interval of at least two weeks must be observed between discontinuation of MAO inhibitor therapy and initiation of Tofranil therapy; this is because of the risk of severe symptoms such as hypertensive crisis, hyperpyrexia, myoclonus, agitation, seizures, delirium and coma (serotoninergic syndrome). The same applies when giving a MAO inhibitor after previous treatment with Tofranil. In both instances Tofranil or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored.

There is evidence to suggest that tricyclic antidepressants may be given as early as 24 hours after withdrawal of a reversible MAO-A inhibitor such as moclobemide. However, the two-week wash-out period must be observed if a MAO-A inhibitor is given after withdrawal of a tricyclic antidepressant.

Selective serotonin re-uptake inhibitors (SSRIs)
Concomitant use may potentiate the effects on the serotoninergic system. SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) may also increase plasma concentrations of imipramine, with corresponding adverse effects. Serotoninergic syndrome: See Interactions with MAO inhibitors above.

Adrenergic neurone blockers
Tofranil may diminish or abolish the antihypertensive effects of guanethidine, betanidine, reserpine, clonidine and alpha-methyldopa. Patients requiring co-medication for hypertension should therefore be given antihypertensives of a different type (e.g. diuretics, vasodilators or beta-blockers).

Sympathomimetics
Tofranil may potentiate the cardiovascular effects of adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine (e.g. in local anaesthetics).

CNS depressants
Tricyclic antidepressants may potentiate the effects of alcohol and other central depressant substances (e.g. opiates, barbiturates, benzodiazepines, general anaesthetics).

Anticholinergic agents
Tricyclic antidepressants may potentiate the effects of these drugs (e.g. phenothiazines, antiparkinsonian agents, antihistamines, atropine and biperiden) on the eyes, CNS, GI tract and bladder. There is also a risk of hyperthermia.

Quinidine
Tricyclic antidepressants should not be employed in combination with antiarrhythmic agents of the quinidine type.

Liver-enzyme inducers
Drugs which activate the hepatic mono-oxygenase enzyme system (e.g. barbiturates, carbamazepine, phenytoin, nicotine and oral contraceptives) may accelerate the metabolism and lower the plasma concentrations of imipramine, resulting in decreased antidepressant effect. Plasma levels of phenytoin and carbamazepine may increase, with corresponding adverse effects. It may be necessary to adjust the dosage of these drugs.

Neuroleptics
Co-medication may result in increased plasma levels of tricyclic antidepressants, a lowered seizure threshold and convulsions. Combination with thioridazine may precipitate severe cardiac arrhythmia.

Anticoagulants
Tricyclic antidepressants may inhibit the hepatic metabolism of coumarin derivatives, thus potentiating their anticoagulant effects. Careful monitoring of plasma prothrombin is therefore advised.

Cimetidine, methylphenidate
These drugs may increase plasma concentrations of tricyclic antidepressants, the dosage of which should therefore be correspondingly reduced.

Oestrogens
There is evidence that oestrogens can sometimes reduce the effects of Tofranil while paradoxically inducing Tofranil toxicity.

OVERDOSAGE
The signs and symptoms of Tofranil overdosage are similar to those reported with other tricyclic antidepressants. The main symptoms are cardiac and neurological disturbances. In children accidental ingestion of Tofranil should be regarded as serious and potentially fatal, whatever the amount.

Signs and symptoms
The first symptoms generally appear within 4 hours of ingestion, with maximum severity after 24 hours. However, owing to protracted absorption (increased anticholinergic effect due to overdosage), the drug's long half-life, and enterohepatic recycling, the patient may be at risk for up to 4–6 days.

The following signs and symptoms may be seen:
Central nervous system: Slight dulling of the senses, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity, choreoathetoid movements, convulsions.

Cardiovascular system: Hypotension, shock, arrhythmia, tachycardia, conduction disorders, heart failure. In very rare cases cardiac arrest.

Others: Respiratory depression, cyanosis, vomiting, fever, mydriasis, sweating, oliguria or anuria.

Management
There is no specific antidote. Treatment is essentially symptomatic and supportive. In all cases of suspected Tofranil overdosage, particularly in children, the patient must be hospitalized and kept under close surveillance for at least 72 hours.

If the patient is fully conscious, perform gastric lavage or induce vomiting as soon as possible. If consciousness is impaired, maintain the airway by means of a cuffed endotracheal tube before beginning lavage and do not induce vomiting. These measures are recommended for up to 12 hours, or even longer, after the overdose, since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help to reduce drug absorption.

Treatment of symptoms is based on modern methods of intensive care, with continuous monitoring of cardiac function, blood gases and electrolytes and, if necessary, emergency measures such as anticonvulsive therapy, mechanical ventilation, temporary use of a cardiac pacemaker, administration of plasma expanders, dopamine or dobutamine by intravenous drip, and resuscitation. Since it has been reported that physostigmine may cause severe bradycardia, asystole and seizures, its use is not recommended in cases of Tofranil overdosage. Haemodialysis and peritoneal dialysis are ineffective because of the drug's high level of protein binding and large volume of distribution.

OTHER INFORMATION
Shelf-life
Store below 30°C and protect from moisture.

Do not use after the expiry date (= EXP) printed on the pack.

PACK SIZES
Country specific pack sizes.

MANUFACTURER
See folding box.

Information last revised: June 1996
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Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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