Imipramine HCl Tablets 25mg USP

1. Name of the medicinal product

Imipramine HCl Tablets 25mg USP Taj Pharma

2. Qualitative and quantitative composition

Each film coated tablet contains:

Imipramine Hydrochloride USP	25mg
Excipients	q.s.

For excipients, see 6.1.

3. Pharmaceutical form

Tablet.

4. Clinical particulars

4.1 Therapeutic indications

1) Treatment of symptoms of depressive illness.

2) Relief of nocturnal enuresis in children.

4.2 Posology and method of administration

Posology

Adults: 1 x 25mg up to three times daily, increasing stepwise to 150-200mg. This should be reached by the end of the first week and maintained until definite improvement has occurred. The subsequent maintenance dose should be individually determined by gradually reducing the dosage, usually to about 50-100mg daily.

In patients in hospital, i.e. severe cases, the dose may be increased to 100mg three times daily until a distinct improvement is seen. Again the subsequent maintenance dose should be determined individually by reducing the dosage, usually to about 100mg daily.

Elderly: Patients over 60 years may respond to lower doses of imipramine than those recommended above. Treatment should be initiated with 10mg daily, gradually increasing to 30-50mg daily. The optimum dose should be reached after about 10 days and then continued until the end of treatment.

Children (for nocturnal enuresis only): The tablets should be administered just before bedtime.

Over 11 years (weight 35-54kg or 77-119lbs): 50-75mg daily.

8-11 years (weight 25-35kg or 55-77lbs): 25-50mg daily.

6-7 years (weight 20-25kg or 44-55lbs): 25mg daily.

Under 6 years: Not to be given to children under 6 years of age.

The dose should not exceed 75mg daily. The maximum period of treatment should not exceed three months, and withdrawal should be gradual. If relapse should occur, treatment should not be re-instituted until a full physical examination has been carried out.

Method of Administration

For oral administration.

4.3 Contraindications

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

• Any degree of heart block or cardiac arrhythmias; recent myocardial infarction;

• Severe liver disease;

• Porphyria;

• Narrow angle glaucoma;

• Urine retention;

• Mania;

• Concomitant treatment with selective, reversible MAO-A inhibitors, *e.g.* moclobemide.

• Children under six years of age.

4.4 Special warnings and precautions for use

Improvement in depression may not occur during the first two to four weeks of treatment and hence patients should be closely monitored during this period.

Hyponatraemia (usually in the elderly) has been associated with all types of antidepressants and should be considered in all patients who develop symptoms such as drowsiness, confusion or convulsions.

As tricyclic antidepressants are known to lower the convulsion threshold, imipramine should be used with extreme caution in patients with epilepsy and other predisposing factors, *e.g.* brain damage of varying aetiology, concomitant use of neuroleptics, withdrawal from alcohol or drugs with anticonvulsive properties (*e.g.* benzodiazepines). Occurrence of seizures appears to be dose-dependent.

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

Caution is required when giving tricyclic antidepressants to patients with severe renal disease.

Caution is required when giving tricyclic antidepressants to patients with tumours of the adrenal medulla (*e.g.* phaeochromocytoma, neuroblastoma), as hypertensive crises may be provoked.

Many patients with panic disorders experience intensified anxiety symptoms 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.

Caution is required in patients with hyperthyroidism or during concomitant treatment with thyroid preparations as aggravation of unwanted cardiac effects may occur.

Before starting treatment it is advisable to check the patients' blood pressure because patients with hypotension or a labile circulation may react to the drug with a fall in blood pressure.

Although changes in the white blood cell count have been reported with imipramine 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. (See section 4.8).

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

Monitoring of cardiac function is indicated in elderly patients.

Because of its anticholinergic properties, imipramine should be used with caution in patients with a history of increased intra-ocular pressure, narrow angle glaucoma, or urinary retention (*e.g.* diseases of the prostate).

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

Before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving imipramine. Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension (see section 4.5).

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.

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.

Imipramine may cause anxiety, feelings of unrest and hyperexcitation in agitated patients and patients with accompanying schizophrenic symptoms.

Activation of psychosis has been observed occasionally in schizophrenic patients receiving tricyclic antidepressants. Hypomanic or manic episodes have also been reported during a depressive phase in patients with cyclic affective

disorders receiving treatment with a tricyclic antidepressant. In such cases it may be necessary to reduce the dosage of imipramine or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with imipramine may be resumed if required.

In predisposed and elderly patients, imipramine may, particularly at night, provoke pharmacogenic (delirious) psychoses, which disappear without treatment within a few days of withdrawing the drug. Agitation, confusion and postural hypotension may occur.

Abrupt withdrawal should be avoided because of possible adverse reactions. (See section 4.8).

Behavioural disturbances may occur in children receiving treatment with imipramine for the treatment of nocturnal enuresis.

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.

4.5 Interaction with other medicinal products and other forms of interaction

• MAO inhibitors (MAOIs): Imipramine should not be administered for at least three weeks after discontinuation of treatment with MAO inhibitors (there is a risk of severe symptoms such as hypertensive crisis, hyperpyrexia, myoclonus, agitation, seizures, delirium and coma). This also applies when giving a MAO inhibitor after previous treatment with imipramine. In both instances imipramine 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 little as 24 hours after a reversible MAO inhibitor such as moclobemide, but the three week wash-out period must be observed if the MAO inhibitor is given after a tricyclic antidepressant has been used.

• Selective serotonin reuptake inhibitors (SSRIs): Co-medication may lead to additive effects on the serotonergic system. Fluoxetine and fluvoxamine may also increase the plasma concentrations of imipramine, with corresponding adverse effects, resulting in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold and seizures.

• CNS depressants: Tricyclic antidepressants may also potentiate the CNS depressant effects of alcohol and central depressant drugs (*e.g.* barbiturates, benzodiazepines or general anaesthetics). (See section 4.4).

• Alprazolam and disulfiram: It may be necessary to reduce the dosage of imipramine if it is administered concomitantly with alprazolam or disulfiram.

• Neuroleptics: Concomitant use may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.

• Adrenergic neurone blockers: Imipramine may diminish or abolish the antihypertensive effects of guanethidine, debrisoquine, bethanidine, reserpine, α-methyldopa and clonidine. Patients requiring co-medication for hypertension should therefore be given antihypertensives of a different type (*e.g.* vasodilators).

• Beta-blockers: Blood concentrations of imipramine may be increased by drugs such as labetalol and propranolol. The clinical importance of these interactions is uncertain.

• Diuretics: Concurrent use of a tricyclic antidepressant and a diuretic may increase the risk of postural hypotension.

• Alpha$_2$-adrenoceptor stimulants: concomitant use of apraclonidine or brimonidine should be avoided.

• Anticoagulants: Tricyclic antidepressants may potentiate the anti-coagulant effect of coumarin drugs by inhibiting hepatic metabolism of anticoagulants. Careful monitoring of plasma prothrombin is therefore advised.

• Anticholinergic agents: Tricyclic antidepressants may potentiate the effects of these drugs (*e.g.* phenothiazine, antiparkinsonian agents, antihistamines, atropine, biperiden) on the eye, central nervous system, bowel and bladder.

• Sympathomimetic drugs: Imipramine may potentiate the cardiovascular effects of adrenaline (epinephrine), ephedrine, isoprenaline, noradrenaline (norepinephrine), phenylephrine and phenylpropanolamine (*e.g.* as contained in local anaesthetic preparations and nasal decongestants).

• Quinidine: Tricyclic antidepressants should not be employed in combination with anti-arrhythmic 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 plasma concentrations of imipramine, resulting in decreased efficacy. Plasma levels of phenytoin and carbamazepine may increase, with corresponding adverse effects. It may be necessary to adjust the dosage of these drugs.

• Cimetidine, methylphenidate: These drugs may increase the plasma levels of imipramine whose dosage should therefore be reduced.

• Oestrogens: There is evidence that oestrogens can sometimes paradoxically reduce the effects of imipramine yet at the same time cause imipramine toxicity.

• Antiviral agents: Drugs such as ritonavir have been reported to increase plasma concentrations of antidepressant drugs.

• Calcium channel blockers: Blood levels of imipramine may be increased by calcium channel blockers such as diltiazem and verapamil.

• Nitrates: Reduced salivary secretion may lessen the effectiveness of sub-lingual nitrate preparations.

• Dopaminergic agents: CNS toxicity may be enhanced when tricyclic antidepressants are used in conjunction with dopaminergic drugs such as selegiline and entacapone.

• Centrally acting appetite suppressants: Concomitant use is not recommended due to the increased risk of CNS toxicity.

• Antineoplastic drugs: concomitant use of altretamine should be avoided due to the risk of severe postural hypotension.

Tricyclic antidepressants may also interact with the following drug classes:

• Analgesics: Possible increase in risk of side effects (nefopam), convulsions (tramadol), sedation (opioid analgesics) or ventricular arrhythmias.

• Anti-arrhythmics: Increased risk of ventricular arrhythmias with drugs, which prolong the QT interval.

• Muscle relaxants: Enhanced muscle relaxant effect of baclofen.

4.6 Pregnancy and lactation

There is no evidence of the safety of the drug in human pregnancy. There have been isolated reports of a possible connection between the use of tricyclic antidepressants and adverse effects (developmental disorders) on the foetus. Treatment with imipramine should be avoided during pregnancy, unless the anticipated benefits justify the potential risk to the foetus.

Neonates whose mothers had taken imipramine up until delivery have developed dyspnoea, lethargy, colic, irritability, hypotension or hypertension, tremor or spasms, during the first few hours or days. If possible, imipramine should be gradually withdrawn at least 7 weeks before the calculated date of confinement.

As imipramine is excreted in breast milk, it should not be administered to nursing mothers unless considered essential when the mother should be advised to cease breast feeding.

4.7 Effects on ability to drive and use machines

Patients should be warned

• That blurred vision, drowsiness and other CNS symptoms (see section 4.8) may occur.

• Against possible hazards such as driving a car, operating machinery or doing anything which may require alertness or quick actions.

• That alcohol or other drugs may potentiate these effects (see section 4.5).

4.8 Undesirable effects

The following frequency estimates are used: frequent >10%, occasional >1-10%, rare >0.001-1%, isolated cases <0.001%

If severe neurological or psychiatric reactions occur, imipramine should be withdrawn.

Elderly patients are particularly sensitive to anticholinergic, neurological, psychiatric, or cardiovascular effects. Their ability to metabolise and eliminate drugs may be reduced, leading to a risk of elevated plasma concentrations at therapeutic doses.

Effects on the central nervous system: fatigue, drowsiness, restlessness, delirium, confusion, disorientation, hallucinations (particularly in geriatric patients and those suffering from Parkinson's disease), increased anxiety, agitation, sleep disturbances, swings from depression to hypomania or mania have been reported occasionally.

Activation of psychotic symptoms has been reported rarely.

In isolated cases aggressiveness has been reported.

Paranoid delusion may be exacerbated during treatment with tricyclic antidepressants. These are more frequently seen in elderly patients or those on high doses.

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

Neurological effects: tremor has been reported frequently.

Paraesthesia, headache and dizziness have been reported occasionally.

Epileptic seizures have been reported rarely.

In isolated cases EEG changes, myoclonus, weakness, extrapyramidal symptoms, ataxia, speech disorders, drug fever has been reported.

Effects on the cardiovascular system: Sinus tachycardia and clinically irrelevant ECG changes (T and ST changes) in patients of normal cardiac status, and postural hypotension have been reported frequently. Cardiac arrhythmias and severe hypotension are likely to occur with high dosage or in deliberate overdosage. They may also occur in patients

with pre-existing heart disease taking normal dosage.

Arrhythmias, conduction disorders (widening of QRS complex and PR interval, bundle-branch block), palpitations have been reported occasionally.

Isolated cases of increased blood pressure, cardiac decompensation, peripheralvasospastic reactions have been reported.

Anticholinergic effects: dry mouth, constipation, sweating, disturbances of visual accommodation, blurred vision, hot flushes have been frequently reported.

Disturbances of micturition have been occasionally reported.

Isolated cases of mydriasis, glaucoma and paralytic ileus have been reported.

Effects on the gastro-intestinal tract:

Nausea, vomiting, anorexia has been reported occasionally.

Isolated cases of stomatitis, tongue lesions, abdominal disorders have been reported.

Hepatic effects: Elevated transaminases have been reported occasionally.

Impaired liver function has been reported rarely.

Isolated cases of hepatitis with or without jaundice have been reported.

Effects on the skin: Allergic reactions (such as urticaria, skin rash) have been reported occasionally.

Isolated cases of oedema (local or generalised), photosensitivity, pruritus, petechiae, hair loss have been reported.

Effects on the endocrine system and metabolism: weight gain has been reported frequently.

Disturbances in libido and potency have been reported occasionally.

Isolated cases of enlarged mammary glands, galactorrhoea, SIADH (syndrome of inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar, weight loss have been reported.

Hyponatraemia, usually in the elderly, has been associated with all types of antidepressants (see section 4.4).

Hypersensitivity: Isolated cases of allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension have been reported.

Effects on the blood: isolated cases of agranulocytosis, bone marrow depression including leucopenia, eosinophilia and thrombocytopenia have been reported. It is advisable to perform blood counts during treatment with tritetracyclic antidepressants, especially if the patient develops fever, sore throat or other signs of infection. (See section 4.4)

Effects on the sense organs: tinnitus has been reported.

Miscellaneous effects: although not indicative of addiction, withdrawal symptoms may occur on abrupt cessation of therapy and include nausea, vomiting, abdominal pain, diarrhoea, headache, insomnia, nervousness, anxiety, irritability and excessive perspiration (see section 4.4).

Respiratory depression, agitation and withdrawal symptoms have been reported in neonates whose mothers received imipramine during the last trimester of pregnancy.

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

<u>Reporting of suspected adverse reactions</u>

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.

4.9 Overdose
The signs and symptoms of overdose with imipramine are similar to those reported with other tricyclic antidepressants. Cardiac abnormalities and neurological disturbances are the main complications. In children accidental ingestion of any amount should be regarded as serious and potentially fatal.

Signs and symptoms: Symptoms generally appear within 4 hours of ingestion and reach a maximum severity after 24 hours. Owing to delayed absorption (increased anticholinergic effect due to overdose), long half-life and enterohepatic recycling of the drug, the patient may be at risk for up to 4-6 days. Major symptoms of overdosage include:

• Effects on the central nervous system: drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity, athetoid and choreiform movements, convulsions.

• Effects on the cardiovascular system include: hypotension, tachycardia, arrhythmia, conduction disorders, heart failure and, in very rare cases, cardiac arrest.

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

Treatment: There is no specific antidote to imipramine. Treatment is essentially symptomatic and supportive. Gastric lavage and forced emesis should be employed immediately if the patient is fully conscious to reduce absorption of the drug. If the patient has impaired consciousness, the airway should be secured with a cuffed endotracheal tube before beginning lavage, and vomiting should not be induced. 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 reduce drug absorption.

Patients presenting with major symptoms of overdosage, particularly children, should be nursed in an intensive care unit for at least 72 hours where full support of vital functions is possible.

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, artificial respiration, insertion of a temporary cardiac pacemaker, plasma expander, dopamine or dobutamine administered by intravenous drip, resuscitation.

Any serious overdosage requires continuous cardiac monitoring for at least 48 hours and dysrhythmias must be treated on an individual basis. Respiratory insufficiency may necessitate intubation and ventilation, and convulsions may be controlled with intravenous diazepam.

Physostigmine should not be used following an overdosage of imipramine as it has been reported that physostigmine may cause severe bradycardia, asystole and seizures. Haemodialysis or peritoneal dialysis is ineffective because of the low plasma concentrations of imipramine.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group

Tricyclic antidepressant.Noradrenaline (NA) and serotonin (5HT) re-uptake inhibitor.

Mechanism of action

Imipramine is a tricyclic antidepressant and has several pharmacological actions including alpha-adrenolytic, antihistamine, anticholinergic and 5HT-receptor blocking properties. However, the main therapeutic activity is believed to be inhibition of the neuronal re-uptake of noradrenaline and 5HT. Imipramine is a so-called “mixed” re-uptake blocker, i.e. it inhibits the reuptake of NA and 5HT to about the same extent.

5.2 Pharmacokinetic properties
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 that also exhibits antidepressant activity.

During oral administration of 50mg 3 times daily for 10 days, the mean steady-state plasma concentrations of imipramine and desmethylimipramine were 33-85ng/ml and 43-109ng/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. Renal impairment is not expected to have any influence on the kinetics of unchanged imipramine and its desmethyl metabolite since both are excreted only in small amounts by the kidneys.

Distribution: About 86% of imipramine binds to plasma proteins. Concentrations of imipramine in the cerebrospinal fluid and the plasma are highly correlated. The mean distribution volume is about 21L/kg.

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

Biotransformation: Imipramine is extensively metabolised in the liver. It is cleared 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 mean half-life of about 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 of these are excreted in the faeces.

Characteristics in patients: Owing to reduced metabolic clearance, plasma concentrations of imipramine are higher in elderly patients than in younger patients.

In children, the mean clearance and elimination of half-life does not differ significantly from adult controls but the between-patient variability is high.

In patients with severe renal impairment, no change occurs in renal excretion of imipramine and its biologically active unconjugated metabolites. However, steady-state plasma concentrations of the conjugated metabolites, which are considered to be biologically inactive are elevated. The clinical significance of this finding is not known.

5.3 Preclinical safety data
Imipramine has no mutagenic or carcinogenic potential. Studies in four species (mouse, rat, rabbit and monkey) led to the conclusion that orally administered imipramine has no teratogenic potential. Experiments with high doses of parenterally administered imipramine resulted mainly in severe maternal and embryotoxic effects, they were thus inconclusive with regard to teratogenic effects.

6. Pharmaceutical particulars

6.1 List of excipients
Carnauba wax, Colloidal silica Gelatin, Lactose, Magnesium stearate, Maize starch, Polyvidone, Stearic acid, Sodium hydroxide.

6.2 Incompatibilities
None known.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 25°C in a dry place.

6.5 Special precautions for disposal and other handling
Not applicable.

7. Manufactured In India By:
TAJ PHARMACEUTICALS LTD.

Mumbai, India
Unit No. 214.Old Bake House,
Maharashtra chambers of Commerce Lane,
Fort, Mumbai - 400001
at:Gujarat, INDIA.
Customer Service and Product Inquiries:
1-800-TRY-FIRST (1-800-222-434 & 1-800-222-825)
Monday through Saturday 9:00 a.m. to 7:00 p.m. EST
E-mail: tajgroup@tajpharma.com