SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Imipramine Tablets BP 10mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active:	Per Tablet
Imipramine hydrochloride BP	10.0mg

3 PHARMACEUTICAL FORM

Sugar coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of depressive illness.

Treatment of nocturnal enuresis in children.

4.2 Posology and method of administration

Adults:

In depressive illness, initially 75mg daily in divided doses increased gradually to 200mg; up to 150mg may be given as a single dose at bedtime.

Children:

In the treatment of nocturnal enuresis 25mg (6-7 years) 25-50mg (8-11 years) or 50-75mg (over 11 years) at bedtime. Dose should be gradually withdrawn over a period of not longer than three months.

Elderly:

Initially 10mg daily, gradually increasing to 30-50mg daily.

4.3 Contraindications

- Hypersensitivity to imipramine, any of the ingredients in the tablets or cross-sensitivity to other tricyclic antidepressants of the dibenzazepine group.
- Recent myocardial infarction
- Any degree of heart block or cardiac arrhythmias.
- Mania
- Porphyria
- Severe liver disease.
- Narrow angle glaucoma.
- Urine retention.
- Concomitant treatment with selective, reversible MAO-A inhibitors, *e.g.* moclobemide.
- Children under six years of age.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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.

Patients posing a high suicide risk require close initial supervision.

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.

Other psychiatric conditions for which imipramine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation 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.

- Alpha2-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, ephedrine, isoprenaline, noradrenaline, 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 Fertility, 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

Mild sedative effects may be observed after the initial dose.

4.8 Undesirable effects

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

If severe neurological or psychiatric reactions occur, Imipramine hydrochloride 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.

The following side effects, although not necessarily observed with imipramine, have occurred with tricylic antidepressants.

(The following frequency estimates are used: 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); Not Known (frequency cannot be estimated from the available data)

Blood and lymphatic system disorders:

Rare: eosinophilia, leucopenia, agranulocytosis, thrombocytopenia and purpura.

Immune system disorders:

Rare: allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension.

Endocrine disorders:

Common: disturbances of libido, impotency or abnormal ejaculation.

Rare: enlarged mammary glands, galactorrhoea, SIADH (syndrome of inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar.

Metabolism and nutrition disorders:

Very common: weight gain

Rare: weight loss

Psychiatric Disorders:

Common: fatigue, drowsiness, restlessness, delirium, confusion, disorientation and hallucination (particularly in geriatric patients and those suffering from Parkinson's disease) increased anxiety, agitation, sleep disturbances, swings from depression to hypomania or mania.

Uncommon: activation of psychotic symptoms

Rare: aggressiveness

Nervous system disorders:

Very common: tremor

Common: paraesthesia, headache, dizziness.

Uncommon: epileptic seizures.

Rare: EEG changes, myoclonus, weakness, extrapyramidal symptoms, ataxia, speech disorder, drug fever.

Ear and labyrinth disorders:

Not known: Tinnitus

Cardiac disorders:

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

Common: arrhythmias, conduction disorders (widening of QRS complex and PR interval, bundle-branch block), palpitations.

Rare: increased blood pressure, cardiac decompensation, peripheral vasospastic reactions.

Gastrointestinal disorders:

Common: nausea, vomiting, anorexia.

Rare: stomatitis, tongue lesions, abdominal disorders

Hepatobiliary disorders:

Common: elevated transaminases

Rare: hepatitis with or without jaundice.

Uncommon: impaired liver function.

Skin and subcutaneous tissue disorders:

Common: allergic skin reactions (skin rash, urticaria)

Rare: oedema (local or generalised), photosensitivity, hyperpigmentation, pruritus, petechiae, hair loss.

Anticholinergic Effects:

Very common: dry mouth, sweating, constipation, disorders of visual accommodation, blurred vision, hot flushes.

Common: disturbances of micturition.

Rare: mydriasis, glaucoma, paralytic ileus.

Withdrawal symptoms:

Common: withdrawal symptoms following abrupt discontinuation of treatment: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness and anxiety.

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.

4.9 Overdose

The first signs of poisoning with tricyclic antidepressants generally take the form of severe anti-cholinergic reactions, which set in about half to two hours after the drug has been taken. The following may be encountered:

- central nervous system - drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity, athetoid and choreiform movements, convulsions.

- cardiovascular system - hypotension, tachycardia, arrhythmia, conduction disorders, heart failure, 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. Physostigmine should not be used 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. Severe poisoning with tricyclic drugs requires immediate hospitalisation and continuous cardiovascular monitoring for at least 48 hours. 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 relapse may occur. The following measures should be taken in cases of overdosage:

- in respiratory failure: intubation and artificial respiration

- in severe hypotension: the patient should be placed in an appropriate position and be given a plasma expander, dopamine or dobutamine by the 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.

Convulsions are also a common symptom of overdosage and may be treated with intravenous diazepam.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Imipramine is a tricyclic antidepressant with actions which include alpha-adrenolytic antihistamine, anticholinergic and 5HT–receptor blocking properties but exhibiting a less marked tendency to cause sedation. Its mode of action in depressive illness is not fully understood but it is believed to be based mainly on its ability to inhibit the neuronal reuptake of noradrenaline and 5HT inhibiting their uptake approx. to the same extent.

5.2 Pharmacokinetic properties

Imipramine is absorbed from the gastrointestinal tract.

It is extensively demethylated in the liver to desipramine. Imipramine and desipramine are extensively bound to tissue and plasma protein.

Imipramine is excreted in the urine mainly as metabolites in either free or conjugated form. Its half-life varies depending on the individual and the dose, but is commonly in the range of 8-19 hours.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (spray dried) BP, Talc BP, Colloidal Anhydrous Silica BP, Stearic Acid BP, Sucrose BP, Titanium Dioxide BP, Dispersed Orange 11348 (Anstead).

6.2 Incompatibilities

None known

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store in a cool dry place.

6.5 Nature and contents of container

100, or 250, or 500 or 1000 tablets contained in High density polypropylene containers with a low density polyethylene closure.

6.6 Special precautions for disposal

No special handling instructions necessary.

7 MARKETING AUTHORISATION HOLDER

Noumed Life Sciences Limited
Noumed House,
Shoppenhangers Road,

Maidenhead,
Berkshire,
SL6 2RB,
United Kingdom

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