SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Imipramine Hydrochloride 25mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Imipramine hydrochloride (N-(γ-dimethylaminopropyl)-iminodibenzyl hydrochloride) 25mg / 5ml in an oral solution formulation

Each 5ml of solution also contains;

Sorbitol (E420)	1050.0	mg
Methyl hydroxybenzoate (E218)	6.85	mg
Propyl hydroxybenzoate (E216)	0.57	mg
Propylene glycol (E1520)	510.4	mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Solution

A clear colourless banana flavoured solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptoms of depressive illness.
Relief of nocturnal enuresis in children.

4.2 Posology and method of administration

Posology

Depression:
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: Patients over 60 years of age may respond to lower doses of Imipramine Hydrochloride 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.

Nocturnal Enuresis in Children:
Not for use in children under 6 years.

6 - 7 years (weight 20-25kg or 44-55lbs)	25mg daily
8 - 11 years (weight 25-35kg or 55-77lbs)	25-50mg daily
Over 11 years (weight 35-54kg or 77-119lbs)	50-75mg daily

A daily dose of 2.5mg/kg should not be exceeded in children. The dose should be taken just before bedtime. The maximum period of treatment should not exceed three months and withdrawal should be gradual. Should a relapse occur, a further course of treatment should not be started until a full physical examination has been made.

Method of administration
For oral administration.

4.3 Contraindications

- Hypersensitivity to imipramine, any of the excipients listed in section 6.1 or cross-sensitivity to other tricyclic antidepressants of the dibenzazepine group.
- Recent myocardial infarction.
- Any degree of heart block or other cardiac arrhythmias.
- Mania.
- Severe liver disease.
- Narrow angle glaucoma.
- Infants and children under 6 years old.
- Retention of urine.
- Concurrent use in patients receiving, or within 3 weeks of cessation of therapy with, monoamine oxidase inhibitors.
- Concomitant treatment with selective, reversible MAO-A inhibitors such as moclobemide.
- Porphyria. Imipramine has been reported to be a porphyrinogenic agent and therefore should be avoided in patients with a known diagnosis or history of porphyria. Patients presenting with psychiatric symptoms in

conjunction with gastrointestinal symptoms or dermatological conditions should be tested for porphyria prior to administration of imipramine. Withdrawal of imipramine upon diagnosis of porphyria or acute porphyria attack should alleviate the symptoms.

4.4 Special warnings and precautions for use

Warnings

As improvement in depression may not occur for the first two to four weeks' of treatment, 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.

Precautions

Tricyclic antidepressants are known to lower the convulsion threshold and Imipramine Hydrochloride should therefore 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). It appears that the occurrence of seizures is dose dependent.

Concomitant treatment of Imipramine Hydrochloride and electroconvulsive therapy should only be resorted to under careful supervision.

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

Serotonin syndrome

Concomitant administration of imipramine and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Caution is called for when giving tricyclic antidepressants to patients with tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), in whom they may provoke hypertensive crises.

Many patients with panic disorders 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.

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

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.

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 enzymes levels is recommended in patients with liver disease. In elderly patients monitoring of cardiac function is indicated.

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

Before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving Imipramine hydrochloride. 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 anticholinergic properties of tricyclic antidepressants may cause damage to the corneal epithelium in patients with contact lenses.

Suicide/suicidal thoughts or clinical worsening
Risk of suicide is inherent to severe depression and may persist until significant remission occurs. 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 posing a high suicide risk require close supervision. 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.

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

Activation of psychosis has occasionally been observed 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 hydrochloride or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with Imipramine hydrochloride may be resumed if required.

In predisposed and elderly patients, Imipramine hydrochloride 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 changes may occur in children receiving Imipramine hydrochloride for treatment of nocturnal enuresis.

Excipient warnings

Imipramine hydrochloride contains:

- Methyl (E218) and propyl hydroxybenzoates (E216), which may cause allergic reactions (possibly delayed).
- Propylene Glycol (E1520). This medicine contains 510.4mg propylene glycol per 5ml dose. While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.
  Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.
- Sorbitol (E420).
  This medicine contains 1050mg sorbitol in each 5ml dose. The additive effect of concomitantly administered products containing sorbitol (or

fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

- This medicine contains less than 1mmol sodium (23mg) per 5ml dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

MAO inhibitors: Do not give Imipramine hydrochloride for at least 3 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). The same applies when giving a MAO inhibitor after previous treatment with Imipramine hydrochloride. In both instances Imipramine hydrochloride or the MAO inhibitors 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 3 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. Fluvoxetine and fluvoxamine may also increase 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 increase the effects of alcohol and central depressant drugs (e.g. barbiturates, benzodiazepines or general anaesthetics). (See section 4.4).

Imipramine should be used cautiously when co-administered with: Buprenorphine/opioids as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

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

Neuroleptics: Co-medication 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 effect of guanethidine, debrisoquine, betanidine, reserpine, clonidine and alpha-methylodopa. Patients requiring co-medication for

hypertension should therefore be given antihypertensives of a different type (e.g. diuretics, vasodilators, or beta blockers).

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 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 these 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 antiarrhythmic agents of the quinidine type.

Liver enzyme inducers: Drugs that 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, terbinafine, amfebutamone: These drugs may increase the plasma concentrations of tricyclic antidepressants, 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

Pregnancy

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 Hydrochloride 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. Imipramine Hydrochloride should if possible be gradually withdrawn at least 7 weeks before the calculated date of confinement.

Breast-feeding

The active substance of Imipramine hydrochloride, imipramine, and its metabolites, desmethylimipramine, pass into the breast milk in small quantities. Imipramine hydrochloride should be gradually withdrawn or the mother advised to cease breast-feeding.

4.7 Effects on ability to drive and use machines

Patients receiving Imipramine Hydrochloride should be warned that blurred vision, drowsiness and other CNS symptoms (see section 4.8) may occur, in which case they should not drive, operate machinery, or do anything which may require alertness or quick actions. Patients should also be warned that alcohol or other drugs may potentiate these effects, (see section 4.5).

4.8 Undesirable effects

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 tricyclic antidepressants.
(The following frequency estimates are used: frequently > 10%, occasionally >1-10%, rarely >0.001-1%, isolated cases <0.001%).

Central Nervous System
Psychiatric Effects:
Occasionally: 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.
Rarely: activation of psychotic symptoms.
Isolated cases: aggressiveness.
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:
Frequently: tremor.
Occasionally: paraesthesia, headache, dizziness.
Rarely: epileptic seizures.
Isolated cases: EEG changes, myoclonus, weakness, extrapyramidal symptoms, ataxia, speech disorder, drug fever.

Cardiovascular System:
Frequently: sinus tachycardia and clinically irrelevant ECG changes (T and ST changes) in patients of normal cardiac status, postural 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.
Occasionally: arrhythmias, conduction disorders (widening of QRS complex and PR interval, bundle-branch block), palpitations.
Isolated cases: increased blood pressure, cardiac decompensation, peripheral vasospastic reactions.

Anticholinergic Effects:
Frequently: dry mouth, sweating, constipation, disorders of visual accommodation, blurred vision, hot flushes.
Occasionally: disturbances of micturition.
Isolated cases: mydriasis, glaucoma, paralytic ileus.

Gastro-Intestinal Tract:
Occasionally: nausea, vomiting, anorexia.
Isolated cases: stomatitis, tongue lesions, abdominal disorders.

Hepatic Effect:
Occasionally: elevated transaminases.
Rarely: impaired liver function.
Isolated cases: hepatitis with or without jaundice.

Skin:
Occasionally: allergic skin reactions (skin rash, urticaria)
Isolated cases: oedema (local or generalised), photosensitivity, hyperpigmentation, pruritus, petechiae, hair loss.

Endocrine System and Metabolism:
Frequently: weight gain.
Occasionally: disturbances of libido, impotency or abnormal ejaculation.
Isolated cases: enlarged mammary glands, galactorrhoea, SIADH (syndrome of inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar, weight loss.
Hyponatraemia, usually in the elderly, has been associated with all types of antidepressants (see section 4.4).

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

Blood:
Isolated cases: agranulocytosis, bone marrow depression including eosinophilia, leucopenia, thrombocytopenia and purpura. 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).

Sense organs:
Tinnitus.

Miscellaneous:
Occasional withdrawal symptoms following abrupt discontinuation of treatment: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, anxiety, irritability and excessive perspiration (see section 4.4).
Contains 1.5g of sorbitol per 5ml spoonful so may cause stomach upset and diarrhoea, particularly at high doses.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

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.

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 and treatment is essentially symptomatic and supportive. Anyone suspected of receiving an overdose of imipramine, particularly children, should be admitted to hospital and kept under close surveillance for at least 72 hours.

Perform gastric lavage or induce vomiting as soon as possible if the patient is fully conscious, to reduce absorption of the drug. If the patient has impaired consciousness, secure the airway with 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 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,
- 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.

Since it has been reported that physostigmine may cause severe bradycardia, asystole and seizures, its use is not recommended in cases of overdosage with imipramine. Haemodialysis or peritoneal dialysis are 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.

ATC Code: N06A A02

Mechanism of action

Imipramine is a tricyclic antidepressant and has several pharmacological actions including alpha-adrenolytic, anti-histaminic, 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 which 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 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

Betacyclodextrin (E459)
Sorbitol solution 70% (E420)
Sodium saccharin (E954)
Hydroxyethylcellulose
Methyl paraben (E218)
Propyl paraben (E216)
Propylene glycol (E1520)
Banana flavour (containing nature identical flavouring substances and mono-propylene glycol as carrier)
Purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years unopened.
30 days once opened.

6.4 Special precautions for storage

Do not store above 25°C. Keep container tightly closed.

6.5 Nature and contents of container

Bottle:	Amber (Type III) glass
Closures:	HDPE, EPE wadded, tamper evident, child resistant closure.
Pack Size:	150ml

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Essential Pharma Limited
8a Crabtree Road, Egham,
Surrey, TW20 8RN,
UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 41871/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

19/03/2025