SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Imipramine 25 mg Tablets BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Imipramine Hydrochloride 25 mg.

Excipients with known effect
Each tablet contains lactose 25.5 mg, sucrose 27.6 mg, sunset yellow (E110) 0.128 mg and sodium benzoate (E211) 0.0011 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.

Biconvex sugar coated reddish brown coloured tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of depressive illness in adults.
For the treatment of nocturnal enuresis in children.

4.2 Posology and method of administration

Posology

Adults:
In depressive illness, initially 75 mg daily given in divided doses and increased gradually to 150-200 mg daily. This dose to be reached by the end of the first week of treatment. Once improvement has occurred a maintenance dose should be calculated, on an individual basis and the dose gradually reduced (normally to approx. 50 – 100 mg daily).

For hospitalized patients the dose can be increased to 100 mg three times daily, until significant improvement occurs. Again a maintenance dose should then be calculated, on an individual basis and the dose reduced (normally to approx. 100 mg daily).

Special populations:

Elderly:
Patients over 60 years of age may be responsive to lower doses than those detailed above. Initially 10 mg daily and gradually increasing the dose to 30 – 50 mg daily. This dose should be reached approximately 10 days after starting treatment and continued for the length of treatment.

Paediatric population:
In the treatment of nocturnal enuresis only:
Do not use in children under 6 years of age (see section 4.3).
6-7 years (weight 20-25 kg or 44-55 lbs): 25 mg at bedtime.
8-11 years (weight 25-35 kg or 55-77 lbs): 25 – 50 mg at bedtime.
11 years and over (weight 35-45 kg or 77-119 lbs): 50 – 75 mg at bedtime.

Do not exceed a daily dose of 2.5 mg/kg. Treatment should not exceed three months and the dose should be gradually withdrawn. Should a relapse occur, no further treatment with imipramine should be started until a full physical examination has been made.

Method of administration

For oral administration.

4.3 Contraindications

- Patients with any degree of heart block or other cardiac arrhythmias; recent myocardial infarction
- Mania
- Severe liver disease
- Porphyria
- Narrow angle glaucoma
- Urine retention

- Hypersensitivity to the active substance imipramine or to any of the excipients listed in section 6.1
- Cross-sensitivity to other tricyclic antidepressants of the dibenzazepine group
- Children under 6 years of age
- Concurrent use in patients receiving or within 3 weeks of stopping treatment with MAO inhibitors
- Concomitant treatment with selective, reversible MAO-A inhibitors such as moclobemide.

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 eg. brain damage of varying aetiology, concomitant use of neuroleptics, withdrawal from alcohol or drugs with anti-convulsive properties (eg benzodiazepines). Occurrence of seizures appears to be dose dependant.

Concomitant treatment with imipramine and electro-convulsive therapy should only be resorted to under careful supervision.

Caution is required when giving tricyclic antidepressants to:
- patients with severe renal disease.
- patients with tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), as hypertensive crisis may be provoked.
- patients with hyperthyroidism or during concomitant treatment with thyroid preparations as aggravation of unwanted cardiac effects may occur.

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 2 weeks.

Before starting treatment it is advisable to check the patient’s 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 those 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 (especially in elderly or bedridden patients).

Before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving imipramine. Anaesthetics given during tri/tetracyclic anti-depressants 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 of this drug 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 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 anti-depressants 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.

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 buprenorphine containing medicinal products 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.

This medicine contains lactose and sucrose
Patients with rare hereditary problems of fructose or galactose intolerance, total lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains sunset yellow (E110) which may cause allergic reactions.

This medicine contains sodium benzoate (E211), giving 0.001 mg benzoate per tablet.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

MAO inhibitors (MAOIs): Imipramine should not be administered 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). 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 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 with imipramine 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 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 dose 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 bethanidine, guanethidine, debrisoquine, α-methyldopa, reserpine 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 labetolol 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 anticoagulant effect of coumarin drugs by inhibiting hepatic metabolism of anticoagulants. Careful monitoring of plasma prothrombin is therefore advised.

Anticholinergic drugs: Tricyclic antidepressants may potentiate the effects of these drugs (eg phenothiazine, anti-parkinsonian agents, antihistamines, atropine, biperiden) on the eye, central nervous system, bowel and bladder.

Sympathomimetic drugs: Imipramine may potentiate the cardiovascular effects of adrenaline (epinephrine), noradrenaline (norepinephrine), ephedrine, isoprenaline, 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 (such as barbiturates, phenytoin, carbamazepine, nicotine and oral contraceptives) may accelerate 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 and methylphenidate: These drugs may increase the plasma levels of imipramine whose dosage therefore should 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 sublingual 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.

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).

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 (development 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 have 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.

Breast-feeding

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

Blurred vision, drowsiness and other CNS symptoms may occur when taking imipramine (see section 4.8), patients should be advised not to drive, operate machinery or do anything requiring alertness or quick actions if affected. Alcohol and other drugs may potentiate these effects (see section 4.5), patients should be advised accordingly.

4.8 Undesirable effects

Imipramine should be withdrawn if severe neurological and psychiatric reactions occur.

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

The following undesirable effects have been reported with tricyclic antidepressant drugs, not necessarily reported with imipramine: Very common (≥1/10), common (≥1/100 - <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 - <1/100), very rare (<1/10,000), frequency not known (cannot be estimated from the available data):

Blood and the lymphatic system disorders:
Very rarely: agranulocytosis, bone marrow depression including eosinophilia, leucopenia and thrombocytopenia have been reported. It is advisable to perform blood counts during treatment with tri/tetracyclic antidepressants, especially if the patient develops fever, sore throat or other signs of infection. (See section 4.4)

Endrocrine disorders:
Very common: weight gain.
Common: changes to libido & potency.
Very rarely: enlarged mammary glands, galactorrhoea, increase/decrease in blood sugar, SIADH (syndrome of inappropriate antidiuretic hormone secretion) and weight loss.

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

Psychiatric disorders:
Common: fatigue, drowsiness, sleep disturbance, increased anxiety, restlessness/agitation, delirium, confusion, swings from depression to hypomania/mania, disorientation and hallucinations (mainly in geriatric patients or those suffering from Parkinson's disease).
Rarely psychotic symptoms have been activated.
Very rarely 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).

Nervous system disorders:
Very common: tremor.
Common: dizziness, headache and paraesthesiae.
Rarely epileptic seizures.
Very rarely ataxia, drug fever, EEG changes, extrapyramidal symptoms, myoclonus, problems with speech and weakness.

Ear and labyrinth disorders:
Tinnitus has been reported.

Cardiac disorders:
Very common: sinus tachycardia and clinically irrelevant ECG changes (T and ST changes) in patients with normal cardiac status, postural hypotension.
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.
Common: arrhythmias, conduction disorders (widening of QRS complex and PR interval, bundle-branch block) and palpitations.
Very rarely increases in blood pressure, cardiac decompensation and peripheral vasospastic reactions.

Gastrointestinal disorders:
Common: anorexia, nausea, vomiting.
Very rarely abdominal disorders, tongue lesions and stomatitis.

Hepato-biliary disorders:
Common: elevated transaminases.
Rarely impaired liver function.
Very rarely hepatitis (with or without jaundice).

Skin and subcutaneous tissue disorders:
Common: allergic skin reactions such as rash and urticaria.
Very rarely oedema (local or generalised), hair loss, photosensitivity, pruritus and petechiae.

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

Anticholinergic effects:
Very commonly (due the anticholinergic action of tricyclic antidepressant drugs) may cause constipation, dry mouth, sweating, hot flushes, blurred vision or disorders of visual accommodation.
Commonly micturition disturbances.
Very rarely glaucoma, mydriasis and paralytic ileus.

Other 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.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 four 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*: agitation, ataxia, athetoid and chorieform movements, coma, convulsions, drowsiness, enhanced reflexes, muscular rigidity, stupor, restlessness.
- *Effects on the cardiovascular system include*: arrhythmia, conduction disorders, heart failure, hypotension, tachycardia and in very rare cases cardiac arrest.
- In addition anuria or oliguria, cyanosis, fever, hydrasis, respiratory depression, shock, sweating and vomiting may occur.

Treatment:

There is no specific antidote, essentially symptomatic and supportive treatment is required. 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. This can be carried out for up to 12 hours or even longer after the overdose (the anti-cholinergic effect of the drug may delay gastric emptying). Activated charcoal can be administered and may help reduce absorption of the drug.

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 electrolyte levels, and if necessary patients can receive emergency measures including anticonvulsive therapy, artificial respiration, insertion of a temporary cardiac pacemaker, given a plasma expander, dopamine or dobutamine by intravenous drip and 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 in cases of imipramine overdose since it may cause asystole, bradycardia or seizures. Haemodialysis or peritoneal dialysis are ineffective due to the low plasma levels of imipramine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
ATC code: N06A A02 – Tricyclic antidepressant. Noradrenaline (NA) and serotonin (5HT) reuptake inhibitor

Mechanism of action
Imipramine is a tricyclic antidepressant and has several pharmacological actions including alpha-adrenolytic, antihistamine, anticholinergic and 5HTreceptor blocking. 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

Lactose (spray dried)
Talc
Colloidal Anhydrous Silica
Stearic Acid
Sucrose
Maize Starch
Spectracoat Brown SP 0897 (containing Sucrose, Titanium Dioxide (E171), Sunset Yellow Aluminium Lake (E110), Erythrosine Aluminium Lake (E127), Indigo Carmine Aluminium Lake (E132), Sodium Benzoate (E211).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Tablet containers: Do not store above 25°C. Keep the container tightly closed.

Blisters: Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

High density polypropylene containers with low density polyethylene caps of 28, 100, 250, 500 & 1000 tablets.

Al/PVC/ blisters enclosed in an outer carton, containing 28 or 56 tablets.

Not all packs may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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