Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tofranil Coated Tablets 25 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg imipramine hydrochloride.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Coated tablets.

Red-brown, biconvex, sugar coated tablet imprinted with the word 'GEIGY'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of endogenous depression, reactive depression, involutional depression; childhood enuresis. As an adjunct in the management of chronic rheumatic pain.

4.2 Posology and method of adminstration

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.

Hospitalised patients i.e. severe cases the dose may be increased to 100mg three times daily until a distinct improvement has been achieved. Again the subsequent maintenance dose should be determined individually by reducing the dosage, usually to about 100mg daily.

Elderly: Patients over 60 years of age may respond to lower doses of Tofranil 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: Not for use in children under 6 years. (For nocturnal enuresis only, in children under 12).

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

A daily dosage 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.

Chronic rheumatic pain: 1 x 25mg three times daily, added to the existing treatment regimen. In patients over 60 years of age 1 x 10mg three times daily will usually provide an adequate therapeutic effect.

4.3 Contraindications

Known hypersensitivity to imipramine and any of the excipients or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group. Recent myocardial infarction. Patients with cardiac arrhythmias, particularly heartblock, severe liver disease, nursing mothers; use in the management of depression in children under 12 years. Concurrent use in patients receiving, or within 3 weeks of cessation of therapy with, monoamine oxidase inhibitors (MAOI). Concomitant treatment with selective, reversible MAO-A inhibitors such as moclobemide is also contraindicated.

4.4 Special warnings and special precautions for use

Tricyclic antidepressants are known to lower the convulsion threshold and Tofranil 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.

Although changes in the white blood cell count have been reported with Tofranil only in isolated cases, periodic blood cell counts and monitoring for symptoms such as fever and sore throat are called for, particularly during the first few months of therapy.

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.

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

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

Patients with cardiovascular disorders, especially those with a history of conduction disorders, as well as in elderly patients. Monitoring of cardiovascular function and ECG is called for in such cases. In order to guard against possible cardiotoxic effects, a daily dosage of 2.5mg/kg should not be exceeded in children.

In elderly patients monitoring of cardiac function is indicated.

Because of its anticholinergic properties, Tofranil 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.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated (see interactions).

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 pithelium in patients with contact lenses.

Risk of suicide is inherent to severe depression and may persist until significant remission occurs. Patients posing a high suicide risk require close supervision.

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 Tofranil or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with Tofranil may be resumed if required.

Abrupt withdrawal should be avoided because of possible adverse reactions (see side effects).

In predisposed and elderly patients, Tofranil 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.

Behavioural changes may occur in children receiving Tofranil for treatment of nocturnal enuresis.

4.5 Interaction with other medicinal products and other forms of interaction

MAO inhibitors: Do not give Tofranil 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 Tofranil. In both instances Tofranil or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored. There is evidence to suggest that tricyclic antidepressants may be given as 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: 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.

Central Nervous System (CNS) depressants: Tricyclic antidepressants may also increase the effect of alcohol and central depressant drugs (e.g. barbiturates, benzodiazepines or general anaesthetics).

Antipsychotic agents may increase the plasma concentrations of imipramine and this can result in serious adverse events. No such effects are known to occur in combination with diazepam.

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

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: Tofranil 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 concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

Estrogens: There is evidence that estrogens can sometimes paradoxically reduce the effects of Tofranil yet at the same time cause Tofranil toxicity.

4.6 Pregnancy and lactation

There is no, or inadequate, evidence of 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 Tofranil should be avoided during pregnancy unless the anticipated benefits justify the potential risks to the foetus.

Neonates whose mothers had taken Tofranil up till delivery have developed dyspnoea, lethargy, colic, irritability, hypotension or hypertension, tremor or spasms, during the first few hours or days. Tofranil should - if this is at all justifiable - be withdrawn at least 7 weeks before the calculated date of confinement.

The active substance of Tofranil and its metabolite desmethylimipramine pass into the breast milk in small quantities. Since nothing is known about the clinical relevance of this, it may be advisable to withdraw the medication or use a breast milk substitute.

4.7 Effects on ability to drive and use machines

Patients receiving Tofranil should be warned that blurred vision, drowsiness and other CNS symptoms (see side effects) 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 interactions).

4.8 Undesirable effects

If severe neurological or psychiatric reactions occur, Tofranil 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 Tofranil, have occurred with tricyclic antidepressants.

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

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

Central Nervous System:
Psychiatric Effects:
Occasionally: fatigue, drowsiness, restlessness, delirium confusion, disorientation and hallucinations (particularly in geriatric patients and those suffering from Parkinson's disease), increased anxiety, agitation, sleep disturbances, swings from depression to hypomania or mania.
Rare: activation of psychotic symptoms.
Isolated cases: aggressiveness.

Neurological Effects:
Frequently: fine tremor.
Occasional: paraesthesiae headache, dizziness.
Rare: epileptic seizures.
Isolated: cases of EEG changes, myoclonus, weakness, extrapyramidal symptoms, ataxia, speech disorders, drug fever.

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

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

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

Hepatic Effects:
Occasional: elevated transaminases
Isolated: cases of hepatitis with or without jaundice.

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

Endocrine System and Metabolism:
Frequent: weight gain
Occasional: disturbances of libido and potency
Isolated: cases of enlarged mammary glands, galactorrhoea, SIADH (syndrome of inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar, weight loss.

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

Blood:
Isolated cases of eosinophilia, leucopenia, agranulocytosis and thrombocytopenia and purpura.

Miscellaneous:
Occasional: withdrawal symptoms following abrupt discontinuation of treatment: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness and anxiety.
Isolated cases of tinnitus.

4.9 Overdose

Children react more sensitively than adults to acute overdosage of tricyclics, and some fatalities have been reported.

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.

Cardiovascular System: Hypotension, tachycardia, arrhythmia, conduction disorders, heart failure; in very rare cases, cardiac arrest.

In addition, respiratory depression, cyanosis, shock, vomiting, fever, mydriasis, 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 relapses 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 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.
- In convulsions: diazepam should be given iv, or another anticonvulsant such as phenobarbitone or paraldehyde (these substances may exacerbate existing respiratory failure, hypotension, or coma).
- Dialysis and haemodialysis are of no use

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Tricyclic antidepressant (ATC code: N06A A02) Noradrenaline (NA) and serotonin (5HT) re-uptake inhibitor.

Mechanism of action
Imipramine is a tricyclic antidepressant and has several pharmacological actions includes alpha-adrenolytic, anti-histaminic, anticholinergic and 5HT-receptor blocking properties. However the main therapeutic activity of imipramine is believed to be inhibition of the neuronal re-uptake of noradrenaline and 5HT. Imipramine is a so called ‘mixed’ reuptake blocker, i.e. it inhibits the re-uptake of NA and 5HT to approximately 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 likewise exhibits antidepressant activity.

During oral administration of 50mg three 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

Core

Colloidal Anhydrous Silica
Lactose
Maize starch
Purified talc

Magnesium stearate
Glycerol
Stearic acid

Coating

Hypromellose
Povidone
Purified talc
Titanium dioxide (E171)

Sugar Coating

Sucrose
Purified talc
Red iron oxide (E172)
Povidone
Macrogol 6000
Microcrystalline cellulose

Polishing solution

Macrogol 6000
Sucrose

Printing Ink

Dispersed red 70752
Permitted colouring opacode brown S-1-9210HV consists of:
Shellac
Black iron oxide (E172)
Yellow iron oxide (E172)
2-ethoxyethanol
Soya lecithin MC thin
Titanium dioxide (E171)
Dimethicone

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Each package contains 6 PVC aluminium blisters each containing 14 Tofranil coated tablets. In total the package contains 84 tablets.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
Frimley Business Park
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Camberley
Surrey, GU16 7SR
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8 MARKETING AUTHORISATION NUMBER

PA 13/86/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1978

Date of last renewal: 1st April 2003

10 DATE OF REVISION OF THE TEXT

May 2004