Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Anafranil 10mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg clomipramine hydrochloride.
Also contains lactose monohydrate, 123.0mg per capsule

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsules
Size No. 4, opaque hard gelatin capsules with a caramel cap and a greyish yellow body imprinted on both cap and body with 'GEIGY' logo and containing a white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of endogenous depression including manic depression, periodic and involutional depression, reactive and neurotic depression, obsessional and phobic states and as an adjunctive treatment of cataplexy associated with narcolepsy.

4.2 Posology and method of administration

Before initiating treatment with Anafranil, hypokalemia should be treated (see 4.4 Special warnings and precautions for use).

As a precaution against possible QTc prolongation and serotonergic toxicity, adherence to the recommended doses of Anafranil is advised and any increase in dose should be made with caution if other serotonergic agents are co-administered (see sections 4.4 Special Warnings and Precautions for use and 4.5 Interaction with other Medicinal Products and other forms of Interaction).

The dosage should be adapted to the individual patient's condition. The aim is to achieve an optimum effect while keeping the doses as low as possible and increasing them cautiously. After a response has been obtained, maintenance therapy should be continued at the optimum dose to avoid relapse. Patients with a history of recurrent depression require maintenance treatment for a longer duration. Duration of maintenance treatment and need for further treatment should be reviewed periodically.

Abrupt discontinuation of Anafranil therapy should be avoided because of possible withdrawal symptoms. Therefore, dosage should be stopped gradually after regular use for long duration and the patient should be monitored carefully when Anafranil therapy is discontinued.

Immediate release formulations (capsules) and sustained-release tablets can be used interchangeably in equivalent doses.

<u>Adults:</u>
Depression:
The usual daily dosage is in the range of 30 to 75mg in single or divided doses. Initial dosage should be 10mg/day with gradual increments to 30-150mg/day in divided doses or as a single dose at bedtime. Dosage may exceed the stated range if necessary up to a maximum of 250mg.

Obsessional/phobic states:
"The maintenance dosage of Anafranil is generally higher than that used in depression. It is recommended that the dose be built up to 100-150mg Anafranil daily, according to the severity of the condition. This should be attained gradually over a period of 2 weeks starting with 1 x 25mg Anafranil daily. In elderly patients and those sensitive to tricyclic antidepressants a starting dose of 1 x 10mg Anafranil daily is recommended. Again where a higher dosage is required the Sustained-release 75mg formulation may be preferable."

Adjunctive treatment of cataplexy associated with narcolepsy:
Initially 10mg, increasing to 50mg daily. Control of cataplexy should be achieved within 24 hours of reaching optimal dose.

Geriatric patients (aged 65 years and older)

Elderly patients generally show a stronger response to Anafranil than patients of intermediate age groups. Anafranil should be used with caution in elderly patients and doses should be increased cautiously. Daily dose should generally be low, initiated at the lowest level (10mg) with very slow cautious increments to 30-75mg daily.

Paediatric Patients
Anafranil is not recommended for use in children due to insufficient data on safety and/or efficacy" (See Section 4.4 Special Warnings and Precautions for use).

Renal imparment:
Anafranil should be given with caution in patients with renal impairment (see section 4.4 special warnings and precautions for use and section 5 pharmacological properties).

Hepatic imparment:
Anafranil should be given with caution in patients with hepatic impairment (see section 4.4 special warnings and precautions for use and section 5 pharmacological properties).

Anafranil prolonged-release tablets should be swallowed whole.
Anafranil can be administered with or without food.

4.3 Contraindications

- Use in patients who are currently receiving, or have received within 3 weeks, monoamine oxidase inhibitors.
- Use in patients in acute recovery phase of myocardial infarction.
- Use in patients hypersensitive to dibenzazepines.
- Use in patients with cardiac arrhythmias, particularly heartblock.
- Use during lactation in women breast-feeding infants.
- Use in mania, severe liver disease, narrow-angle glaucoma, and retention of urine.
- Use in patients with congenital QT syndrome.

4.4 Special warnings and precautions for use

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 Anafranil 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 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.

Modifying the therapeutic regimen, including possibly discontinuing the medication, should be considered in these patients, especially if these changes are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Prescriptions for Anafranil should be written for the smallest quantity of tablets or capsules consistent with good patient management, in order to reduce the risk of overdose.

Other psychiatric effects
Many patients with panic disorder experience more marked anxiety at the start of treatment with Anafranil. This paradoxical initial increase in anxiety is most pronounced during the first few days of treatment and generally subsides within two weeks.
Activation of psychosis has occasionally been observed in patients with schizophrenia 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 Anafranil or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with Anafranil may be resumed if required.
In predisposed patients, tricyclic antidepressants may provoke pharmacogenic (delirious) psychoses, particularly at night. These disappear within a few days of withdrawing the drug.

Cardiac and vascular disorders
Anafranil should be administered with particular caution in patients with cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders, (e.g. atrioventricular block grades I to III), or arrhythmias. Monitoring of cardiac function and the ECG is indicated in such patients. There may be a risk of QTc prolongation and Torsades de Pointes, particularly at supratherapeutic doses or supra-therapeutic plasma concentrations of clomipramine, as occur in the case of co-medication with selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenergic reuptake inhibitors (SNaRIs). Therefore, concomitant administration of drugs that can cause accumulation of clomipramine should be avoided equally, concomitant administration of drugs that can prolong the QTc interval should be avoided (see sections 4.2 Posology and method of administration and 4.5. interactions with other medicinal products and other forms of interaction). It is established that hypokalaemia is a risk-factor of QTc prolongation and Torsades de pointes. Therefore, hypokalaemia should be treated before initiating treatment with Anafranil and Anafranil should be used with caution when combined with SSRIs, SNaRIs or diuretics (see section 4.5)

Tricyclic antidepressants are known to lower the convulsion threshold and Anafranil 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, therefore the recommended total daily dose of Anafranil should not be exceeded.

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

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

Elderly patients are particularly liable to experience adverse effects, especially agitation, confusion, and postural hypotension.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency of glucose-galactose malabsorption should not use this medication.

Precautions
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.

White blood cell count
Although changes in the white blood cell count have been reported with Anafranil 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. They are also recommended during prolonged therapy.
It is advisable to monitor cardiac and hepatic function during long-term therapy with Anafranil. In patients with hepatic and renal disease, periodic monitoring of the hepatic enzyme levels and renal function is recommended.

Anticholinergic effects
Because of its anticholinergic properties, Anafranil 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).

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

Caution should be exercised when using Anafranil in patients with severe renal disease.

In elderly patients, tricyclic antidepressants may provoke pharmacogenic (delirious) psychoses, particularly at night. These disappear within a few days of withdrawing the drug.

Monitoring of cardiac function and the ECG is indicated in elderly patients.

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.

Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available. Anafranil is not recommended for use in children due to insufficient data on safety and/or efficacy".

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

Decreased lacrimation and accumulation of mucoid secretions due to the anticholinergic properties of trycyclic antidepressants may cause damage to the corneal epithelium 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 initial supervision.

Anaesthesia
Before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving Anafranil and of the possible interactions (see 4.5 Interaction with other medicaments and other forms of interaction).

Treatment discontinuation
Abrupt withdrawal should be avoided because of possible adverse reactions (see 4.8 Undesirable Effects). If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see section 4.8 Undesirable effects, for a description of the risks of discontinuation of Anafranil).

4.5 Interaction with other medicinal products and other forms of interaction

Adrenergic neurone blockers: Anafranil may diminish or abolish the antihypertensive effects of guanethidine, betanidine, reserpine, clonidine and alpha-methyldopa. Patients requiring comedication for hypertension should therefore be given antihypertensives of a different type (e.g. vasodilators, or beta-blockers).

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.

CNS depressants: Tricyclic antidepressants may potentiate the effects of alcohol and other central depressant substances (e.g. barbiturates, benzodiazepines, or general anaesthetics).

Diuretics: Comedication of Anafranil with diuretics may lead to hypokalemia, which in turn increases the risk of QTc prolongation and Torsades de Pointes. Hypokalaemia should therefore be treated prior to administration of Anafranil (see 4.2 Posology and 4.4 Special warnings and precautions).

MAO inhibitors: Do not give Anafranil for at least 3 weeks after discontinuation of treatment with MAO inhibitors (there is a risk of severe symptoms such as hypertensive crisis, hyperpyrexia and those consistent with Serotonin Syndrome e.g. myoclonus, agitation, seizures, delirium and coma). The same applies when giving a MAO inhibitor after previous treatment with Anafranil. In both instances the treatment should initially be given in small gradually increasing doses and its effects monitored. There is evidence to suggest that Anafranil may be given as little as 24 hours after a reversible MAO-A inhibitor such as moclobemide, but the 3 week wash-out period must be observed if the MAO-A inhibitor is used after Anafranil.

Selective serotonin reuptake inhibitors: Co-medication with SSRI's may lead to additive effects on the serotonin system, (see serotonergic agents).

Serotenergic Agents: Seretonin Syndrome can possible occur when clomipramine is administered with serotonergic co-medications such as selective serotonin re-uptake inhibitors (SSRIs), serotonin and nonadrenergic reuptake inhibitors SNaRI's), tricyclic antidepressants –or lithium. For fluoxetine, a washout period of two to three weeks is advised before and after treatment with fluoxetine.

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

Pharmacokinetic-related interactions: Anafranil (clomapramine) is predominantly eliminated through metabolism. The primary route of metabolism is demethylation to form the active metabolite, N-desmethylclomipramine, followed by hydroxylation and further conjugation of both N-desmethylclomipramine and the parent drug. Several cytochrome P450's are involved in the desmethylation, mainly CYP3A4, CYP2C19 and CYP1A2. Elimination of both active components is by hydroxylation and it's catalyzed by CYP2D6.

Concomitant administration of CYP2D6 inhibitors may lead to an increase in concentration of both active components, up to ~3 fold in patients with desbrinoquine/sparteine extensive metabolizer phenotype, converting them to poor-metabolizer phenotype. Concomitant administration of CYP1A2, CYP2C19 and CYP3A4 inhibitors are expected to increase clomipramine concentrations and decrease N-desmethylclomipramine, thus not necessarily affecting the overall pharmacology.

- MAO inhibitors which are also potent CYP2D6 inhibitors in vivo, such as moclobemide, are contraindicated for coadministration with clomipramine.

- Antiarrhythmics (such as quinidine and propafenone), which are potent inhibitors of CYP2D6, should not be used in combination with tricyclic antidepressants.

- SSRI's, which are inhibitors of CYP2D6, such as fluoxetine, paroxetine or sertraline and of others including CYP1A and CYP2C19 (e.g. Fluvoxamine) may also increase plasma concentrations of clomipramine, with corresponding adverse effects. Steady-state serum levels of clomipramine increased ~4 fold by co-administration of fluvoxamine (N-desmethylclomipramine decreased ~ 2 fold).

- Comedication of antipsychotics (e.g.phenothiazines) may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.

- Oral antifungal, terbinafine. Coadministration of Anafranil with terbinafine, a strong inhibitor of CYP2D6, may result in increased exposure and accumulation of clomipramine and its N-demethylated metabolite. Therefore, dose adjustments of Anafranil may be necessary when coadministered with terbinafine.

- Coadministration with the histamine$_2$ (H_2) receptor antagonist, cimetidine (an inhibitor of several P450 enzymes, including CYP2D6 and CYP3A4), may increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

- No interaction between chronic oral contraceptive use (15 or 30 mg ethinyl estradiol daily) and Anafranil (25 mg daily) has been documented. Estrogens are not known to be inhibitors of CYP2D6, the major enzyme involved in clomipramine clearance and therefore, no interaction is expected. Although in a few cases with high dose estrogen (50 mg daily) and the tricyclic antidepressant imipramine, increased side effects and therapeutic response were noted, it is unclear as to the relevance of these cases to clomipramine and lower dose estrogen regimens. Monitoring therapeutic response of tricyclic antidepressants at high dose estrogen regimems (50 mg daily) is recommended and dose adjustments may be necessary.

- Methylphenidate (e.g. Ritalin) may also increase concentrations of tricyclic antidepressants by potentially inhibiting their metabolism, and a dose reduction of tricyclic antidepressant may be necessary.

- Concomitant administration of valproate with clomipramine may cause inhibition of CYP2C and/or UGT enzymes resulting in increased serum levels of clomipramine and desmethylclomipramine.

- Concomitant administration of Anafranil with grapefruit, grapefruit juice or cranberry juice my increase the plasma concentrations of clomipramine.

- Some tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs, such as warfarin, and this may be through inhibition of their metabolism (CYP2C9). There is no evidence for the ability of clomipramine to inhibit the metabolism of anticoagulants, such as warfarin, however, careful monitoring of plasma prothrombin has been advised for this class of drug.

- Concomitant administration of drugs known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19, and/or CYP1A2 may accelerate the metabolism and decrease the efficacy of Anafranil.

- CYP3A and CYP2C inducers such as rifampicin or anticonvulsants (e.g. barbiturates, carbamazepine, phenobarbital and phenytoin), may decrease clomipramine concentrations.

- Known inducers of CYP1A2 (e.g. nicotine/components in cigarette smoke), decrease plasma concentrations of tricyclic drugs. In cigarette smokers, clomipramine steady-state plasma concentrations were decreased 2 fold compared to non-smokers (no change in N-desmethylclomipramine).

- Concomitant administration of ion exchange resins such as cholestyramine or colestipol may reduce the plasma levels of clomipramine. Staggering the dosage of clomipramine and resins, such that the drug is administered at least 2 h before or 4-6 h after the administration of resins, is recommended.

- Concomitant administration of Anafranil with St. John's wort during the treatment may decrease the plasma concentrations of clomipramine.

Clomipramine is also an in vitro (K_i = 2.2µM) and in vivo inhibitor of CYP2D6 activity (sparteine oxidation) and therefore, may cause increased concentrations of co-administered compounds that are primarily cleared by CYP2D6 in extensive metabolizers.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
There are no data supporting any special recommendations in women of child-bearing potential.

Pregnancy
There is limited amount of data from the use of Anafranil in pregnant women that indicates a potential to harm the foetus or cause congenital malformation. Anafranil should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Neonates whose mothers had taken tricyclic antidepressants until delivery showed drug withdrawal symptoms, such as dyspnoea, lethargy, colic, irritability, hypotension or hypertension, and tremor /convulsions, during the first few hours or days. To avoid such symptoms, Anafranil should if possible be gradually withdrawn at least 7 weeks before the calculated date of confinement.

Lactation
Since the active substance passes into breast milk, Anafranil should be gradually withdrawn or the infant weaned if the patient is breast-feeding.

Fertility
No adverse effects on reproductive performance, including male and female fertility, were observed in rats at oral doses up to 24 mg/kg.
No teratogenic effects were detected in mice, rats, and rabbits at doses up to 100, 50, and 60 mg/kg, respectively (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Patients receiving Anafranil should be warned that blurred vision, and other nervous system and psychiatric related disorders such as somnolence, disturbance in attention, confusion, disorientation, aggravation of depression, delirium etc, (see Undesirable Effects), have been observed. In the presence of such effects, patients should not drive or operate machinery or do anything else which may require alertness or quick actions.

4.8 Undesirable effects

Unwanted effects are usually mild and transient, disappearing under continued treatment or with a reduction in the dosage. They do not always correlate with plasma drug levels or dose. It is often difficult to distinguish certain undesirable effects from symptoms of depression such as fatigue, sleep disturbances, agitation, anxiety, constipation, and dry mouth.

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

Frequency estimates: Very common ≥ 10%, common ≥1% to <10%, uncommon ≥ 0.1% to <1%, rare ≥ 0.01% to <0.1%, very rare <0.01%. The ADRs listed below are based on clinical trials as well as post marketing reports.

Blood and lymphatic system disorders
Very rare leukopenia, agranulocytosis, thrombocytopenia, eosinophilia

Cardiac disorders

Common	sinus tachycardia, palpitations, orthostatic hypotension, clinically irrelevant ECG changes (e.g. ST and T changes) in patients of normal cardiac status
Uncommon	arrhythmias, blood pressure increased
Very rare	conduction disorders (e.g. widening of QRS complex, prolonged QT interval, PQ changes, bundle-branch block, Torsade de Pointes, particularly in patients with hypokalaemia)

Ear and labyrinth disorders

Common	tinnitus

Endocrine disorders

Very rare	SIADH (inappropriate antidiuretic hormone secretion syndrome)

Eye disorders

Very common	accomodation disorder, vision blurred
Common	mydriasis
Very rare	glaucoma

Gastrointestinal disorder

Very common	nausea, dry mouth, constipation
Common	vomiting, gastrointestinal disorder, diarrhoea

General disorders and administration site conditions

Very common	fatigue
Very rare	oedema (local or generalised), alopecia, hyperpyrexia

Hepatobiliary disorders

Very rare	hepatitis with or without jaundice.

Immune system disorders

Very rare	systemic anaphylactic and anaphylactoid reactions including hypotension

Investigations

Very common	weight increased
Common	transaminases increased
Very rare	electroencephalogram abnormal

Metabolism and nutrition disorders

Very common	increased appetite
Common	decreased appetitie

Musculoskeletal and connective tissue disorders

Common	muscular weakness

Nervous system disorders

Very common	dizziness, tremor, headache, myoclonus, somnolence
Common	speech disorders, paraesthesia, hypertonia, dysgeusia, memory impairment, disturbance in attention
Uncommon	convulsions, ataxia
Very rare	neuroleptic malignant syndrome

Psychiatric disorders

Very common	restlessness
Common	confusional state, disorientation, hallucinations (particularly in elderly patients and patients with Parkinson's disease), anxiety, agitation, sleep disorder, mania, hypomania, aggression, depersonalisation, aggravation of depression, insomnia, nightmares, delirium

Uncommon	activation of psychotic symptoms
Unknown	suicidal ideation* and suicidal behaviour*

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

Renal and urinary disorders

Very common	micturition disorder
Very rare	urinary retention

Reproductive system and breast disorders

Very common	libido disorder, erectile dysfunction
Common	galactorrhoea, breast enlargement

Respiratory, thoracic and mediastinal disorders

Common	yawning
Very rare	alveolitis (pneumonitis) with or without eosinophilia

Skin and subcutaneous tissue disorders

Very common	hyperhidrosis
Common	dermatitis allergic (skin rash, urticaria), photosensitivity reaction, pruritus
Very rare	purpura

Vascular disorders

Common	hot flush

Additional adverse drug reaction from port-marketing spontaneous reports

The following additional adverse drug reactions have been identified with Anafranil oral or IM/IV dosage forms based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Nervous system disorders

Frequency not known: Serotonin syndrome, extrapyramidal symptoms (including akathisia and tardive dyskinesia)

Musculoskeletal and connective tissue disorders

Frequency not known: Rhabdomyolysis (as a complication of neuroleptic malignant syndrome)

Reproductive system and breast disorders

Frequency not known: Ejaculation failure, Ejaculation delayed

Investigations

Frequency not known: Blood prolactin increased

Bone fractures

Epidemiological studies, mainly 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 the risk is unknown

Withdrawal symptoms

The following symptoms commonly occur after abrupt withdrawal or reduction of the dose: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, and anxiety.

Geriatric population

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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The signs and symptoms of overdose with Anafranil 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 maximum severity after 24 hours. Owing to delayed absorption (anticholinergic effect), long half-fife, and enterohepatic recycling of the drug, the patient may be at risk for up to 4-6 days.

The following signs and symptoms may be seen:

Central nervous system
Somnolence, stupor, coma, ataxia, restlessness, agitation, hyperreflexia, muscular rigidity and choreoathetosis movements, convulsions. In addition, symptoms consistent with Serotonin Syndrome (e.g. hyperpyrexia, myoclonus, delirium and coma) may be observed.

Cardiovascular system
Hypotension, tachycardia, arrhythmias, QTc prolongation and arrhythmias including Torsades de Pointes, conduction disorders, shock, heart failure; in very rare cases cardiac arrest.

Respiratory depression, cyanosis, vomiting, fever, mydriasis, sweating, and oliguria or anuria may also occur.

Treatment
There is no specific antidote, and treatment is essentially symptomatic and supportive.

Anyone suspected of receiving an overdose of Anafranil, particularly children, should be hospitalised and kept under close surveillance for at least 72 hours.

Perform gastric lavage or induce vomiting as soon as possible if the patient is alert. If the patient is not alert, 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 ever longer after the overdose, since the anticholinergic effect of the drug may help to reduce drug absorption.

Since it has been reported that phyotigmine may cause severe bradycardia, asystole, and seizures, it’s use is not recommended in cases of overdosage with Anafranil. Haemodialysis or peritoneal dialysis are ineffective because of the low plasma concentrations of clomipramine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Tricyclic antidepressant, ATC code: N06A A04

Mechanism of action
The pharmacological action includes alpha-adrenolytic, anticholinergic, anti-histaminic and 5-HT receptor blocking properties. The main property displayed by the compound is its ability to inhibit the neuronal re-uptake of noradrenaline and 5-HT. Inhibition of the latter is the dominant component.

5.2 Pharmacokinetic properties

Absorption:
The active substance is completely absorbed following oral administration and intramuscular injection.

The systemic bioavailability of unchanged clomipramine is reduced by 50% by hepatic "first-pass" metabolism to desmethylclomipramine (an active metabolite). Following single dose administration 25 mg coated tablet and 75 mg sustained release tablet, the mean maximum plasma concentration (Cmax) of clomipramine were 63.37 ± 12.71 ng/mL (Tmax 4.83 ± 0.39 hr) and 32.55 ± 8.10 (Tmax 9.00 ± 1.81 hr), respectively. The dose of 75mg Anafranil daily produces steady state concentrations of clomipramine ranging from about 20 to 175ng/ml. The steady state plasma concentrations of he active metabolit N-desmethylclomipramine follow a similar pattern but are 40-85% higher than those of clomipramine.

Distribution:
Clomipramine is 97.6% bound to plasma proteins. Clomipramine is extensively distributed throughout the body with the apparent volume of distribution of about 12-17 L/kg bodyweight. Concentrations in cerebrospinal fluid are about 2% of the plasma concentration. Clomipramine passes into maternal milk in concentrations similar to those in plasma and crosses the placenta.

Metabolism:
The primary route of clomipramine metabolism is demethylation to form the active metabolite, N-desmethylclomipramine. N-desmethylclomipramine can be formed by several P450 enzymes, primary CYP3A4, CYP2C19, and CYP1A2. Clomipramine and N-desmethylclomipramine are hydroxylated to form 8-hydroxyclomipramine or 8-hydroxy-N-desmethylclomipramine. Clomipramine is also hydroxylated at the 2-position and N-desmethylclomipramine can be further demethylated to form didesmethylclomipramine. The 2- and 8-hydroxy metabolites are excreted primarily as glucuronides in the urine. Elimination of the active components, clomipramine and N-desmethylclomipramine, by formation of 2-and 8-hydroxy clomipramine is catalysed by CYP2D6.

Elimination:
Oral clomipramine is eliminated from the blood with a mean half-life of 21 hours (range 12-36 h), and desmethylclomipramine with a half-life of 36 hours.

About two-thirds of a single dose of clomipramine is excreted in the form of water-soluble conjugates in the urine, and approximately one-third in the faeces. The quantity of unchanged clomipramine and desmethylclomipramine excreted in the urine amounts to about 2% and 0.5% of the administered dose respectively.

Food effect
Food has no significant impact on the pharmacokinetics of clomipramine. A slight delay in the onset of absorption may be observed with the administration of Anafranil with food.

Dose proportionality
The drug follows dose-proportionate pharmacokinetics over a dose range of 25 to 150 mg.

Effect of age
In elderly patients, clomipramine has relatively low clearance in comparison to younger adult patients. It is reported to reach a therapeutic steady state at doses lower than that reported for middle-age patients. Clomipramine should be used with caution in elderly patients.

Renal impairment
There are no specific reports describing the pharmacokinetic of the drug in patients with renal impairment. Although the drug is excreted as inactive metabolites in the urine and faeces, the accumulation of inactive metabolites may subsequently result in the accumulation of the parent drug and its active metabolite. In moderate and severe renal impairment, it is recommended to monitor the patient during the treatment.

Hepatic impairment
Clomipramine is extensively metabolized in the liver by CYP2D6, CYP3A4, CYP2C19 and CYP1A2, hepatic impairment may impact on its pharmacokinetics. In patients with liver impairment, clomipramine should be administered with caution.

Ethnic sensitivity
Although the impact of ethnic sensitivity and race on the pharmacokinetics of clomipramine has not been studied extensively, the metabolism of clomipramine and its active metabolite is governed by genetic factors leading to poor and extensive metabolism of the drug and its metabolite. The metabolism of clomipramine in Caucasians population may not be extrapolated to Asians, in particular, Japanese and Chinese because of the pronounced differences of metabolism of clomipramine between these two ethnic groups.

Sustained release formulation
Sustained release of clomipramine from Anafranil sustained release formulation provides a smoother pharmacokinetic profile by maintaining therapeutic plasma concentrations over 24 hours. Maximum mean plasma concentrations are reached within about 9 hours post-dose. Following administration of 75 mg clomipramine as sustained release formulation, observed Cmax is half the maximum concentration levels reached after administration of 25 mg tablets three times a day. Nevertheless, the total exposure remains unchanged. Following multiple administration of sustained release formulation, Cmin and Cmax levels attained at steady state are within the therapeutic range. Sustained-release tablets are bioequivalent with coated tablets and capsules.

5.3 Preclinical safety data

Repeat-dose toxicity

Phospholipidosis and testicular changes, commonly associated with tricyclic compounds, have been observed with clomipramine hydrochloride at doses $\geq$10 fold greater than the maximum recommended human daily dose (MRHD).

Reproductive toxicity

No adverse effects on reproductive performance, including male and female fertility, were observed in rats at oral doses up to 24 mg/kg.
No teratogenic effects were detected in mice, rats, and rabbits at doses up to 100, 50, and 60 mg/kg, respectively.

Mutagenicity

Various *in vitro* and *in vivo* mutagenicity tests were performed and did not reveal any mutagenic activity of clomipramine hydrochloride.

Carcinogenicity

There was no evidence of carcinogenicity in mice and rats after 104 weeks of treatment with clomipramine hydrochloride.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Magnesium stearate
Lactose monohydrate

Capsule
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide black (E172)
Iron oxide red (E172)
Gelatin

Printing Ink
Opacode brown S-I- 26593:
Shellac
Industrial methylated spirits
Iron oxide red (E172)
Iron oxide black (E172)
Titanium Dioxide (E171)
Propylene glycol
Isopropyl alcohol
N-butyl alcohol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister packs in cardboard cartons.

Pack sizes of 100 capsules and 84 capsules are available.

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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