SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Anafranil 25 mg
Anafranil SR 75 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Anafranil 25 mg, coated tablets:
1 coated tablet contains 25 mg clomipramine hydrochloride.
Excipients with known effect: each coated tablet contains 15 mg lactose monohydrate and 16.5 mg sucrose.

Anafranil SR 75 mg tablets, slow release tablets:
1 slow release tablet contains 75 mg clomipramine hydrochloride.
Excipient with known effect: each slow release tablet contains 0.2 mg macrogolglycerol hydroxystearate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Anafranil 25 mg:
Lightly yellow, round, biconvex, sugar-coated tablets.

Anafranil SR 75 mg:
Pink, capsule shaped, biconvex, film-coated tablets, scored on both sides. One side debossed with 'C/G' and the other 'G/D'.

Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders.
Anyone considering the use of clomipramine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need.
Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.
Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.
Clomipramine hydrochloride is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD) (see Special warnings and precautions for use, Suicide/suicidal thoughts or clinical worsening).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:
Depression of varying origin.
Obsessive-compulsive syndromes.

Children and adolescents (5-18 years old):
Obsessive-compulsive syndromes.

4.2 Posology and method of administration

Oral use.

Before initiating treatment with Anafranil, hypokalemia should be treated (see section 4.4 Warnings and precautions).

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.

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 drugs that prolong QT interval or other serotonergic agents are co-administered (see sections 4.4 Warnings and precautions and 4.5 Interactions).

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 (coated tablets) and slow-release tablets can be used inter-changeably in equivalent doses.

Adults

Depression and obsessive-compulsive syndromes

Start treatment with 50-75 mg/day (1 coated tablet of 25 mg 2-3 times daily or 1 slow-release tablet of 75 mg once daily [preferably in the evening]). Raise the daily dosage stepwise, e.g. 25 mg every few days, (depending on how the medication is tolerated) to 100-150 mg, during the first week of treatment. In severe cases, this dosage can be increased up to a maximum of 250 mg daily. Once there is a distinct improvement, adjust the daily dosage to a maintenance level of about 50-100 mg.

Dosage and administration in special populations

Geriatric population

For elderly patients, alternative treatments should be considered.

Children aged 5 years and older and adolescents (see also section 4.4)

Adolescents generally show a stronger response to Anafranil than patients of intermediate age groups. Anafranil should be used with caution in adolescents and doses should be increased cautiously.
Obsessive-compulsive syndromes

No experience is available in children under 5 years.

The starting dose is 25 mg daily and should be gradually increased (also given in divided doses) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller.

Depression of varying origin
In children and adolescents, there is not sufficient evidence of safety and efficacy of Anafranil in the treatment of depressive states of varying aetiology and symptomatology. The use of Anafranil in children and adolescents (0-17 years of age) in this indication is therefore not recommended.

Renal impairment

Anafranil should be given with caution in patients with renal impairment (see section 4.4 Warnings and precautions).

Hepatic impairment
Anafranil should be given with caution in patients with hepatic impairment (see section 4.4Warnings and precautions).

Method of administration
The method of administration should be adapted to the individual patient's condition. The Divitabs (slow-release tablets divisible) can be halved, allowing the dosage to be adapted individually, but they should not be chewed.
Anafranil can be administered with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance, other tricyclic antidepressants of the dibenzazepine group or any of the excipients listed in section 6.1.
- Antiarrhythmics such as quinidine and propafenone, which are potent CYP2D6 inhibitors, must not be combined with tricyclic antidepressants.
- Clopiramine must not be given in combination, or within 21 days before or after treatment, with a MAO inhibitor (also see section 4.5). The concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated.
- Recent myocardial infarction
- Cardiac arrhythmias
- Congenital long QTc syndrome.
- Narrow-angle glaucoma
- Acute urinary retention
- Severe hepatic disease

4.4 Special warnings and precautions for use

Anaphylactic shock
Single cases of anaphylactic shock have been reported.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with a higher risk of suicidal thinking, self-damaging behaviour, and suicide (suicidality).

The risk persists until significant remission of the symptoms of depression occurs.
Patients should be monitored closely until remission because the recovery of the symptoms does not take place during the first weeks of treatment. General clinical experience has shown an increased risk of suicide during the early stages of remission.

Other psychiatric disorders which are treated with Anafranil could also lead to a higher risk of suicidality. In addition, such incidents could also occur together with a depressive disorder (episodes of a major depression).

When treating other psychiatric disorders, the same precautions should be maintained as when treating a depressive disorder.

The risk of suicidal thinking or suicide attempts is higher in patients with suicidality in their medical history or in patients who have been extremely suicidal before starting the treatment. Such patients should be monitored closely during the treatment. A meta-analysis of placebo-controlled studies with antidepressants in adults with psychiatric disorders have shown a higher risk of suicide in patients younger than 25 years compared to placebo.

Patients should be closely monitored during the initial phase of therapy or at times of dose changes, especially those patients with a higher risk.
Patients (and their caregivers) should be alerted about the need to monitor clinical worsening, suicidal behaviour or thinking and unusual changes in behaviour closely and in case of such symptoms seek medical advice immediately.

Patients with depressive disorders, both adult and paediatric, may experience worsening of depression and/or suicidality or other psychiatric symptoms, whether or not they are taking antidepressant medication. Antidepressants increased the risk of suicidal thinking and behaviour (suicidality) in short-term studies in children, adolescents and young adults with depressive disorders and other psychiatric disorders.

When modifying the therapeutic regimen, including possibly discontinuation, those symptoms should be considered, especially if they are distinct or occur abruptly or are not part of the basic symptoms of the disorder (see “Treatment discontinuation” in the same section). Prescriptions for Anafranil should be written for the smallest quantity of tablets and patients should be closely monitored to reduce the risk of an overdose. Anafranil has been reported to be associated with fewer deaths following overdose than other tricyclic antidepressants.

Other psychiatric effects

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 the product 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
Tricyclic antidepressants should be administered with 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 supra- therapeutic 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 (SNRIs) (see sections 4.2 and 4.5). Therefore, concomitant administration of drugs that can cause accumulation of clomipramine should be avoided (see sections 4.2 and 4.5). It is established that hypokalemia is a risk-factor of QTc prolongation and torsades de pointes. Therefore, hypokalemia should be treated before initiating treatment with Anafranil (see section 4.2 and 4.5). Before starting treatment, it is advisable to check blood pressure because patients with postural hypotension or a labile circulation may experience a fall in blood pressure.

Serotonin syndrome

Due to the risk of serotonergic toxicity, it is advisable to adhere to the recommended doses. Concomitant administration of clopramine and other serotonergicagents such as Selective Serotonin re-Uptake Inhibitors (SSRIs), Serotonin Noreepinephrine Re-Uptake Inhibitors (SNRIs), tricyclic antidepressants, Buprenorphine or lithium may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5)

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities (myoclonus, seizures), gastrointestinal symptoms, hyperpyrexia, agitation, delirium, and coma.

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

A washout period of two to three weeks is advised before and after treatment with this fluoxetine.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Convulsions
Tricyclic antidepressants are known to lower the convulsion threshold. Anafranil should, therefore, be used with extreme caution in patients with epilepsy and other predisposing factors, e.g., brain damage of varying etiology, 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.

Tricyclic antidepressants should be given with electroconvulsive therapy only under careful supervision.

Anticholinergic effects
Because of its anticholinergic properties, Anafranil should be used with caution in patients with a history of increased intraocular pressure, narrow-angle glaucoma, or urinary retention (e.g., diseases of the prostate).

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.

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

Caution is indicated in patients with hyperthyroidism or patients receiving thyroid preparations, owing to the possibility of enhanced cardiac toxicity due to its anticholinergic properties.

In patients with hepatic and renal disease, periodic monitoring of the hepatic enzyme levels and renal function is recommended.

Caution is called for in patients with chronic constipation when treated with Anafranil because it may cause paralytic ileus, particularly in elderly and in bedridden patients.

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

Control of cardiovascular functions and the ECG are necessary 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.

Blood count
Although changes in the white blood cell count have been reported only in isolated cases, periodic blood cell counts and monitoring for symptoms such as fever, sore throat and other symptoms of a flu-like infection are called for, particularly during the first few months of therapy and during prolonged treatment.

Anesthesia
Before general or local anesthesia, the anesthetist should be told that the patient has been receiving Anafranil (see section 4.5).

Treatment discontinuation
Abrupt withdrawal should be avoided because of possible adverse reactions. 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 serious symptoms (see section 4.8).

Lactose and sucrose
Anafranil 25 mg coated tablets contain lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, total lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Castor oil
Anafranil SR 75 mg slow release tablets contain castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in a contraindication
MAO inhibitors
If clomipramine should be administered after treatment with MAO inhibitors, *a washout period of at least 21 days is advised* (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 clomipramine. In both cases Anafranil or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored until the patient has reached the optimal dosage (see section 4.3).

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 21 days washout period must be observed if the MAO-A inhibitor is

given after Anafranil has been used. MAO inhibitors such as moclobemide, are not suitable for concomitant treatment with Anafranil as CYP2D6 inhibitors (see section 4.3).

Interactions resulting in a concomitant use not recommended

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

Diuretics
Diuretics may lead to hypokalaemia, which in turn increases the risk of QTc prolongation and torsades de pointes. Hypokalaemia should therefore be treated prior to administration of Anafranil (see sections 4.2 and 4.4).

Selective serotonin reuptake inhibitors (SSRIs)
SSRIs are strong inhibitors of CYP2D6 (such as fluoxetine, paroxetine, or sertraline), CYP1A2 and CYP2C19 (e.g., fluvoxamine) and may 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) (see sections 4.2 and 4.4).
Comedication with SSRIs may lead to additive effects on the serotonergic system.

Serotonergic Agents
The risk of serotonin syndrome, a potentially life-threatening condition, is increased when clomipramine is administered with serotonergic co-medications such as selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenergic reuptake inhibitors serotonin norepinephrine re-uptake inhibitors (SNRIs), tricyclic antidepressants, buprenorphine or lithium (see sections 4.2 and 4.4). A washout period of two to three weeks is advised before and after treatment with fluoxetine.

Interactions to be considered

Interactions resulting in increased effect of Anafranil
Concomitant administration of CYP2D6 inhibitors may lead to an increase in concentration of both active components, up to ~3-fold in patients with a debrisoquine/sparteine extensive metabolizer phenotype, converting them to a 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.

Terbinafine
Oral antifungal terbinafine. Co-administration 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 co-administered with terbinafine.

Cimetidine
Co-administration 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.

Oral contraceptives
No interaction between long-term oral contraceptive use (15 or 30 micrograms 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 micrograms 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 regimens (50 micrograms daily) is recommended and dose adjustments may be necessary.

Antipsychotics
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.

Methylphenidate
Methylphenidate, such as ritaline, may increase concentrations of tricyclic antidepressants by potentially inhibiting their metabolism and a dose reduction of the tricyclic antidepressant may be necessary.

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

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

Interactions resulting in decreased effect of Anafranil

Rifampicin
Rifampicin (CYP3A and CYP2C inducer) may decrease clomipramine concentrations as concomitant administration of drugs known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19, may accelerate the metabolism and decrease the efficacy of Anafranil.

Anticonvulsants
Anticonvulsants (CYP3A and CYP2C inducer) (e.g., barbiturates, carbamazepine, phenobarbital, and phenytoin), may decrease clomipramine concentrations as concomitant administration of drugs known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19, may accelerate the metabolism and decrease the efficacy of Anafranil.

Cigarette smoking
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).

Colestipol and cholestyramine
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.

St. John's wort
Concomitant administration of Anafranil with St. John's wort during the treatment may decrease the plasma concentrations of clomipramine.
Interactions affecting other drugs

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.

Antiadrenergic agents
Tricyclic antidepressants may diminish or abolish the antihypertensive effects of clonidine, guanethidine, betanidine, reserpine, and alpha-methyldopa. If necessary, antihypertensives of a different type should be given (e.g., vasodilators, or beta- blockers).

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

Sympathomimetic drugs
Tricyclic antidepressants may potentiate the cardiovascular effects of sympathomimetic drugs, such as adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine (e.g., local anaesthetics containing sympathomimetic drugs).

Anticoagulants
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 blood coagulation has been advised for this class of drug.
Clomipramine is also an *in vitro* (K_i = 2.2 microM) and *in vivo* inhibitor of CYP2D6 activity (sparteine oxidation) and therefore, may cause increased plasma concentrations of co-administered compounds that are primarily cleared by CYP2D6 in extensive metabolisers.

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/spasms/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.

Breast-feeding
Since the drug passes into the breast milk, the medicinal product 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

This medicinal product has a major impact on the 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, aggravation of depression, delirium etc. (see section 4.8) have been observed. In the presence of such effects, patients should not drive, operate machinery, or do anything else requiring alertness. Patients should also be warned that alcohol or other drugs may potentiate these effects (see section 4.5).

4.8 Undesirable effects

Summary of the safety profile
Unwanted effects do not always correlate with plasma drug levels or dose. It is often difficult to distinguish certain undesirable effects from symptoms of the treated disorder (depression) such as fatigue, sleep disturbances, agitation, anxiety, constipation, and dry mouth.

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

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

Adverse reactions are ranked under heading of system organ class and frequency: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000); not known (frequency cannot be estimated from the available data).

The ADRs tabulated below are based on clinical trial results as well as post- marketing reports.

Blood and lymphatic system disorders	
Very rare	Leukopenia, agranulocytosis, thrombocytopenia, eosinophilia
Immune system disorders	
Very rare	Anaphylactic and anaphylactoid reactions including hypotension
Endocrine disorders	
Very rare	Inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	
Very common	Increased appetite, weight gain
Psychiatric disorders	
Very common	Restlessness, libido disorder, erectile dysfunction
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, nervousness
Uncommon	Activation of psychotic symptoms
Not known	Suicidal thinking and behaviour (single cases of suicidal thinking and behaviour have been reported during or shortly after treatment with clomipramine (also see section 4.4.)).
Nervous system disorders	
Very common	Fatigue, light-headedness, dizziness, tremor, headache, myoclonus,
Common	Memory impairment, disturbance in attention, speech disorder, paraesthesia, hypertonia, dysgeusia
Uncommon	Convulsions, ataxia
Very rare	EEG changes, neuroleptic malignant syndrome
Eye disorders	
Very common	Accommodation disorder, vision blurred
Common	Mydriasis
Very rare	Glaucoma

Ear and labyrinth disorders	
Common	Tinnitus
Cardiac disorders	
Common	Sinus tachycardia, palpitation
Uncommon	Arrhythmias
Very rare	Conduction disorder (e.g. widening of QRS complex, prolonged QT interval, PQ changes, bundle-branch block, torsade de pointes, particularly in patients with hypokalaemia)
Vascular disorders	
Common	Hot flush, orthostatic hypotension
Very rare	Hypotension
Respiratory, thoracic, and mediastinal disorders	
Common	Yawning
Very rare	Alveolitis allergic (pneumonitis) with or without eosinophilia
Gastrointestinal disorders	
Very common	Dry mouth, constipation, nausea,
Common	Vomiting, gastrointestinal disorder, diarrhoea, decreased appetite
Hepatobiliary disorders	
Very rare	Hepatitis with or without jaundice
Skin and subcutaneous tissue disorders	
Very common	Hyperhidrosis
Common	Allergic dermatitis (skin rash, urticaria), photosensitivity reaction, pruritus
Very rare	Alopecia, purpura
Musculoskeletal and connective tissue disorders	
Common	Muscular weakness, muscle hypertonia
Renal and urinary disorders	
Very common	Micturition disorder
Very rare	Urinary retention
Reproductive system and breast disorders	
Very common	Erectile dysfunction
Common	Galactorrhoea, breast enlargement
General disorders and administration site conditions	
Very common	Fatigue
Very rare	Hyperpyrexia, oedema (local or generalised)
Investigations	
Very common	Weight increased
Common	Clinically irrelevant ECG changes (e.g., ST and T changes) in patients of normal cardiac status, transaminases increased
Uncommon	Increased blood pressure
Very rare	Conduction disorder (e.g., widening of QRS complex, prolonged QT interval, PQ changes), electroencephalogram abnormal

Additional adverse drug reactions from post-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 disorder (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.

Class effect
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs or tricyclic antidepressants. The mechanism leading to this risk is unknown.

Withdrawal symptoms
The following symptoms commonly occur after abrupt withdrawal of clomipramine or reduction of the dose: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, anxiety (see section 4.4).

Geriatric population
Elderly patients are particularly sensitive to anticholinergic, neurological, psychiatric, or cardiovascular effects. Their ability to metabolize 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: /https://sideeffects.health.gov.il.

4.9 Overdose

The 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.
Symptoms
The first signs and symptoms generally appear within 4 hours of ingestion and reach maximum severity after 24 hours. Owing to delayed absorption (anticholinergic effect), long half-life, and enterohepatic recycling of the drug, the patient may be at risk for up to 4-6 days.

The following symptoms may be seen:
Central nervous system

Somnolence, stupor, coma, ataxia, restlessness, agitation, hyperreflexia, muscler rigidity and choreoathetosis, convulsions. In addition, symptoms consistent with serotonin syndrome (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 even longer after the overdose since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help to reduce drug absorption.

Since it has been reported that physostigmine may cause severe bradycardia, asystole, and seizures, its use is not recommended in cases of overdosage with Anafranil.
Peritoneal dialyses or haemodialyses are ineffective because of the low plasma concentrations of clomipramine.

Rare cases of pharmacobezoar, (masses of undigested or indigestible material) of varying severity, including fatal outcome, have been reported in association with overdose of prolonged-release Anafranil. The pharmacobezoar may be radiopaque, facilitating radiologic (X-ray or CT scan) confirmation but cannot exclude the diagnosis. The formation of pharmacobezoar may cause slow but continual release and absorption of clomipramine which may lead to overdose complications, including death, hours after drug ingestion and initial treatment with gastric lavage and activated charcoal. Since gastric lavage may be ineffective and could further increase systemic drug levels, consideration should be given to physical removal of the pharmacobezoar by endoscopy or surgery in selected patients. Since these cases are very rare, there is insufficient clinical data regarding optimal treatment which should take into account the size and location of the pharmacobezoar, patient symptoms and condition and drug levels.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidepressant, non-selective monoamine reuptake inhibitors
ATC code: N06AA04

Mechanism of action
Clomipramine is a tricyclic antidepressant, which therapeutic activity is believed to be based on its ability to inhibit the neuronal reuptake of noradrenaline (NA) and serotonin (5-HT) released in the synaptic cleft, with inhibition of 5-HT reuptake being the more important of these activities. Clomipramine also has a wide pharmacological spectrum of action, which includes alpha$_1$-adrenolytic, anticholinergic, antihistaminic, and anti-serotonergic (5-HT-receptor blocking) properties.

Pharmacodynamic effects
Anafranil acts on the depressive syndrome as a whole, including in particular typical features such as psychomotor retardation, depressed mood, and anxiety. The clinical response usually sets in after 2-3 weeks of treatment.
Clomipramine also exerts a specific effect on obsessive-compulsive disorder distinct from its antidepressant effects.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, clomipramine is completely absorbed from the gastrointestinal tract.
The systemic bioavailability of unchanged clomipramine is reduced to about 50% by first-pass metabolism to the active metabolite, *N*-desmethylclomipramine.

Following single dose administration of Anafranil 25 mg coated tablet and Anafranil 75 mg sustained-release tablet, the mean maximum plasma concentration (C_{max}) of clomipramine were 63.37 ± 12.71 ng/mL (T_{max} 4.83 ± 0.39 hr) and 32.55 ± 8.10 ng/mL (T_{max} 9.00 ± 1.81 hr), respectively. The recommended dose for treatment of depression, which is 75 mg daily, administered either as coated tablets of 25 mg t.i.d. or as a sustained-release tablet of 75 mg once daily, produces steady-state plasma concentrations ranging from about 20 to 175 ng/mL.

The steady-state concentrations of the active metabolite *N*-desmethylclomipramine follow a similar pattern. However, at a dose of 75 mg Anafranil per day, the metabolite levels 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 distribution volume is about 12 to 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 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 catalyzed by CYP2D6.

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

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

Proportinality of dosage
The drug shows dosage-proportional pharmacokinetics in a dosage 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 feces, 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 metabolised 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.

Formulations with sustained release
The sustained release of clomipramine from a sustained-release tablet leads to a lower pharmacokinetic profile, because therapeutic plasma concentrations are maintained over 24 hours. The maximal mean plasma concentrations are attained after 9 hours after administration. After administration of Anafranil 75 mg sustained-release tablets, reported C_{max} maintains half the values of C_{max} after administration of Anafranil 25 mg coated tablets 3-times daily, however, the total expostion remains unchanged. C_{min} and C_{max}, which are maintained in steady-stade, lie within the therapeutic range after several administrations of Anafranil sustained-release. Anafranil coated tablets and sustained-release tablets are bioequivalent.

Clinical trials
There are currently no clinical trials performed with Anafranil.

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 >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

Anafranil 25mg:
Sucrose, Lactose monohydrate, Talc, Maize starch, Silica colloidal anhydrous, Stearic acid, Magnesium stearate, Glycerol 85%, Hypromellose, Vinylpyrrolidone, Povidone, Titanium dioxide (CI 77891, E 171), Titanium dioxide, Polyethylene glycol 8000, Cellulose microcrystalline, Iron oxide yellow (CI 77492, E 172).

Anafranil SR 75mg tablets:
Calcium hydrogen phosphate dihydrate, Polyacrylate dispersion 30%, Calcium stearate, Hypromellose, Talc, Silica, colloidal anhydrous, Castor oil, hydrogenated, Pigment suspension white: Titanium dioxide (CI 77891, E171), Hypromelose (E464), Pigment suspension red: Iron oxide, red (CI 77491, E172), Hypromelose (E464).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

Keep in the original carton in order to protect from moisture.

6.5 Nature and contents of container

Anafranil 25 mg: 30 coated tablets in PVC blister packs.

Anafranil SR 75 mg tablets: 20 slow release tablets in PVC blister packs.

7. Registration holder and importer:

Tzamal Bio-Pharma, 20 Hamagshimim St., Kiryat Matalon, Petah Tikva

8. Registration numbers:

Anafranil 25 mg: 108-06-24600-00
Anafranil SR 75 mg tablets: 053-91-26407-00

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