SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Anafranil  50mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Chemical name: 3-chloro-5-[3-(dimethylamino)-propyl] 10, 11- dihydro-5H-
dibenz [b,f] azepine hydrochloride (= clomipramine hydrochloric).

Each capsule contains 50mg clomipramine hydrochloride B.P.

For excipients see section 6.1 List of excipients

3 PHARMACEUTICAL FORM

Capsule

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Symptoms of depressive illness especially where sedation is required. Obsessional and phobic states. Adjunctive treatment of cataplexy associated with narcolepsy.

Children and Adolescents
In children and adolescents, there is not sufficient evidence of safety and efficacy of Anafranil in the treatment of depressive states, phobias and cataplexy associated with narcolepsy. The use of Anafranil in children and adolescents (0-17 years of age) in these indications is therefore not recommended (see section 4.4 Special Warnings and Precautions for use).

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).

After a response has been obtained, maintenance therapy should be continued at the optimum dose to avoid relapse. Patients with a history of recurrence 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 Special Warnings and Precautions for use and 4.5 Interaction with other Medicinal Products and other forms of Interaction).

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.

**Adults:** Oral - 10mg/day initially, increasing gradually to 30-150mg/day, if required, in divided doses throughout the day or as a single dose at bedtime. Many patients will be adequately maintained on 30-50mg/day. Higher doses may be needed in some patients, particularly those suffering from obsessional or phobic disorders. In severe cases this dosage can be increased up to a maximum of 250mg per day. Once a distinct improvement has set in, the daily dosage may be adjusted to a maintenance level of about 50-100mg.

**Elderly:** 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. The initial dose should be 10mg/day, which may be increased with caution under close supervision to an optimum level of 30-75mg daily which should be reached after about 10 days and then maintained until the end of treatment.

**Children and Adolescents (0-17 years of age):** Not recommended (see section 4.4 Special Warnings and Precautions for use).

**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 SR 75mg formulation may be preferable.

**Adjunctive treatment of cataplexy associated with narcolepsy:** (Oral treatment): 10-75mg daily. It is suggested that treatment is commenced with 10mg Anafranil daily and gradually increased until a satisfactory response occurs. Control of cataplexy should be achieved within 24 hours of reaching the optimal dose. Where necessary, therapy may be combined with capsules up to the maximum dose of 75mg per day.

**Treatment discontinuation**
Abrupt withdrawal should be avoided because of possible adverse reactions. If the decision is 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 4.4 Special Warnings and Precautions for use and section 4.8 Undesirable effects, for a description of the risks of discontinuation of Anafranil).

Renal impairment
Anafranil should be given with caution in patients with renal impairment (see section 4.4 Warnings and precautions and 5.0 Pharmacological Particulars)

Hepatic impairment
Anafranil should be given with caution in patients with hepatic impairment (see section 4.4 Warnings and precautions and 5.0 Pharmacological Particulars).

Route of Administration
Oral

4.3 Contraindications

Known hypersensitivity to clomipramine, or any of the excipients or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group. Recent myocardial infarction. Any degree of heart block or other cardiac arrhythmias. Mania, severe liver disease, narrow angle glaucoma. Retention of urine. Anafranil must not be given in combination or within 3 weeks before or after treatment with a MAO inhibitor (see section 4.5 Interactions with other Medicinal Products and other forms of Interaction). The concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobamide, is also contra-indicated.

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.

**Use in Children and Adolescents (0-17 years of age)**
Anafranil should not be used in the treatment of depressive states, phobias and cataplexy associated with narcolepsy in children and adolescents under the age of 18 years (see section 4.1 Therapeutic indications).

Antidepressants increase the risk of suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominately aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long term safety data in children and adolescents concerning growth, maturation and cognitive behavioural development are lacking.

Families and caregivers of both paediatric and adult patients being treated with antidepressants for both psychiatric and non psychiatric indications, should be alerted about the need to monitor patients for the emergence of other psychiatric symptoms (see section 4.8 Undesirable effects), as well as the emergence of suicidality, and to report such symptoms immediately to health care providers.

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

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.

**Other Psychiatric Effects**
Many patients with panic disorders experience intensified anxiety symptoms at the start of the treatment with antidepressants. This paradoxical initial increase in anxiety is most pronounced during the first few days of treatment and generally subsides within two weeks.
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.

As improvement in depression may not occur for the first two to four weeks treatment, patients should be closely monitored during this period.

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

**Cardiac and Vascular Disorders**
Anafranil should be administered with particular precaution in patients with cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders, (e.g. atrioventricular block grades I to III), arrhythmias. Monitoring of cardiac function and the ECG is indicated in such patients.

There may be a risk of QTc prolongation and Torsade 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). 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 section 4.5 Interactions with other Medicinal Products and other forms of Interaction). It is established that hypokalemia is a risk-factor of QTc prolongation and Torsade de Pointes. Therefore, hypokalemia should be treated before initiating treatment with Anafranil (see section 4.5 Interactions with other Medicinal Products and other forms of Interaction.)

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.

**Serotonin Syndrome**
Due to the risk of serotonergic toxicity, it is advisable to adhere to recommended doses. Serotonin syndrome, with symptoms such as hyperpyrexia, myoclonus, agitation, seizures, delirium and coma, can possibly occur when clomipramine is administered with serotonergic co-medications such as SSRIs SNRIs, tricyclic antidepressants or lithium. Therefore, concomitant administration of drugs that can cause accumulation of clomipramine 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). For fluoxetine a washout period of two to three weeks is advised before and after treatment with fluoxetine.

**Convulsions**
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.

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

**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).

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 tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), in whom they may provoke hypertensive crises.

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

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.

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.

Caution is called for in patients with chronic constipation. Tricyclic antidepressants may cause paralytic ileus, particularly in the 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.
Monitoring of cardiac function and the ECG is indicated in elderly patients.

**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.

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

**Treatment Discontinuation**
Abrupt withdrawal should be avoided because of possible adverse reactions. If the decision is 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).

Patients with rare hereditary problems of galactose intolerance, fructose intolerance, severe lactase deficiency, sucrase-isomaltase insufficiency or glucose-galactose malabsorption should not take Anafranil capsules.

4.5 Interaction with other medicinal products and other forms of interaction

**Interactions resulting in a contraindication**

**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 consistent with Serotonin Syndrome such as hypertensive crisis, hyperpyrexia, 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.

**Interactions resulting in a concomitant use not recommended**

**Diuretics**
Diuretics may lead to hypokalemia, which increases the risk of QTc prolongation and Torsade de Pointes, Hypokalaemia should therefore be
treated prior to administration of Anafranil (see sections 4.2 Posology and Method of Administration and 4.4 Special Warnings and Precautions for Use).

**Quinidine**
Tricyclic antidepressants should not be employed in combination with antiarrhythmic agents of the quinidine type.

**Selective serotonin reuptake inhibitors (SSRIs)**
SSRIs which are inhibitors of CYP2D6, such as fluoxetine, paroxetine, or sertraline, and of others including CYP1A2 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). In addition, comedication with SSRIs may lead to additive effects on the serotonergic system (see serotonergic agents). (See sections 4.2 Posology and Method of Administration and 4.4 Special Warnings and Precautions for use).

**Serotonergic Agents**
Serotonin Syndrome can possibly occur when Anafranil is administered with other serotonergic co-medications such as selective serotonin reuptake inhibitors (SSRI’s), serotonin and noradrenergic reuptake inhibitors (SNaRI’s), tricyclic antidepressants and lithium (see sections 4.2 Posology and Method of Administration and 4.4 Special Warnings and Precautions for use). For fluoxetine 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**

**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.

**Cimetidine**
Coadministration with the histamine2 (H2)-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 chronic 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 antipsychotic (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**
This drug may also increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

**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-desmethyloclopamiprine)

**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).

**Antidepressive agents**
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).

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

**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).

**Anticoagulants**
Tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs by inhibiting their metabolism by the liver. Careful monitoring of plasma prothrombin is therefore advised.

**Drugs that can cause increase plasma clomipramine levels or which in themselves prolong the QTc interval**
The risk of QTc prolongation and Torsade de Pointes is likely to be increased if Anafranil is co-administered with other drugs that can cause QTc prolongation. Therefore concomitant use of such agents with Anafranil is not recommended (see section 4.4 Special Warnings and Precautions for use). Examples include certain anti-arrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone and sotalol), tricyclic antidepressants (such as amitriptyline); certain tetracyclic antidepressants (such as maprotiline); certain antipsychotic medications (such as phenothiazines and pimozide); certain antihistamines (such as terfenadine); lithium, quinine and pentamidine. This list is not
exhaustive. The risk of QTc prolongation and Torsade de Pointes is likely to be increased if Anafranil is co-administered with drugs that can cause increased plasma clomipramine levels. Anafranil is metabolised by cytochrome P450 2D6 and the plasma concentration of Anafranil may therefore be increased by drugs that are either substrates and/or inhibitors of this P450 isoform. Therefore, concurrent use of these drugs with Anafranil is not recommended (see section 4.4 Special Warnings and Precautions for use). Examples of drugs which are substrates or inhibitors of cytochrome P450 2D6 include anti-arrhythmics, certain antidepressants including SSRIs, tricyclic antidepressants and moclobemide; certain antipsychotics; β-blockers; protease inhibitors, opiates, ecstasy (MDMA), cimetidine and terbinafine. This list is not exhaustive.

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.

Neonates whose mothers had taken tricyclic antidepressants until delivery have developed dyspnoea, lethargy, colic, irritability, hypotension or hypertension, tremor or spasms, during the first few hours or days.

Studies in animals have shown reproductive toxicity (see section 5.3).

Anafranil is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
The active substance of Anafranil passes into the breast milk in small quantities. Therefore nursing mothers should be advised to withdraw the medication or cease breast-feeding.

Fertility
Clomipramine hydrochloride did not appear to have any significant effects on fertility and general reproductive performance.

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 section 4.8 Undesirable Effects) have been observed. In the presence of such effects, patients should not drive, operate machinery or do anything else which may require alertness or quick actions. Patients should also be warned that alcohol or other drugs may potentiate these effects (see section 4.5 Interaction with other Medicinal Products and other forms of Interaction).
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.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10) common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), unknown (frequency cannot be estimated from available data).

Table 1

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Leukopenia, agranulocytosis, thrombocytopenia, eosinophilia</td>
</tr>
</tbody>
</table>

Cardiac disorders

<table>
<thead>
<tr>
<th>Common</th>
<th>Sinus tachycardia, palpitation, orthostatic hypotension, clinically irrelevant ECG changes (e.g. ST and T changes) in patients of normal cardiac status</th>
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</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Arrhythmias, blood pressure increased</td>
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<tr>
<td>Very rare</td>
<td>Conduction disorder (e.g. widening of QRS complex, prolonged QT interval, PQ changes, bundle-branch block, torsade de pointes, particularly in patients with hypokalaemia)</td>
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</table>

Ear and labyrinth disorders

<table>
<thead>
<tr>
<th>Common</th>
<th>Tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Inappropriate antidiuretic hormone secretion (SIADH)</td>
</tr>
</tbody>
</table>

Endocrine disorders

| Very rare                             | Inappropriate antidiuretic hormone secretion (SIADH) |

Eye disorders

| Very common                           | Accommodation disorder, vision blurred |
| Common                                | Mydriasis |
| Very rare                             | Glaucoma |

Gastrointestinal disorders

| Very common                           | Nausea, dry mouth, constipation |
| Common                                | Vomiting, gastrointestinal disorders, 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: Anaphylactic and anaphylactoid reactions including hypotension

#### Investigations
- Very common: Weight increased
- Common: Transaminases increased
- Very rare: Electroencephalogram abnormal
- Unknown: Blood prolactin increased

#### Metabolism and nutrition disorders
- Very common: Increased appetite
- Common: Decreased appetite

#### Musculoskeletal and connective tissue disorders
- Common: Muscular weakness
- Unknown: Rhabdomyolysis (as a complication of neuroleptic malignant syndrome)

#### Nervous system disorders
- Very common: Dizziness, tremor, headache, myoclonus, somnolence
- Common: Speech disorder, paraesthesia, hypertonia, dysgeusia, memory impairment, disturbance in attention
- Uncommon: Convulsions, ataxia
- Very rare: Neuroleptic malignant syndrome
- Unknown: Serotonin syndrome, extrapyramidal disorder (including akathisia and tardive dyskinesia)

#### 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, suicidal behaviours

#### Renal and urinary disorders
- Very common: Micturition disorder
- Common: 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 allergic (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 |

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1. In post-marketing experience very rarely malignant neuroleptic syndrome has been reported although a causal relationship has not been confirmed.
2. Cases of suicidal ideation and suicidal behaviours have been reported during Anafranil therapy or early after treatment discontinuation (see section 4.4).
3. These adverse events were reported in patients treated with Anafranil based on post marketing reports.

#### 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 (see 4.4 Special Warnings and Precautions for use).

#### Class effects
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown.

#### Elderly 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

### 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.
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 signs and symptoms may be seen:

**Central nervous system:**
- Somnolence, stupor, coma, ataxia, restlessness, agitation, hyperreflexia, muscle rigidity, choreoathetosis, convulsions, serotonin syndrome (e.g. hypertensive crisis, hyperpyrexia, myoclonus, delirium and coma) may be observed.

**Cardiovascular system**
- Hypotension, tachycardia, QTc prolongation and arrhythmia including Torsade 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 has impaired consciousness, secure the airway with a cuffed endotracheal tube before beginning lavage, and do not induce vomiting. These measures are recommended for up to 12 hours or even longer after the overdose, since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help to reduce drug absorption.
- **Treatment of Torsade de Pointes.**
  - If Torsade de Pointes should occur during treatment with Anafranil, the drug should be discontinued and hypoxia, electrolyte abnormalities and acid base disturbances should be corrected. Persistent Torsade de Pointes may be treated with magnesium sulphate 2g (20ml of 10% solution) intravenously over 30-120 seconds, repeated twice at intervals of 5-15 minutes if necessary. Alternatively, if these measures fail, the arrhythmia may be abolished by increasing the underlying heart rate. This can be achieved by atrial and ventricular pacing or by isoprenaline (isoproterenol) infusion to achieve a heart rate of 90-110 beats/minute. Torsade de Pointes is usually not helped by antiarrhythmic drugs and those which prolong the QTc interval (e.g. amiodarone, quinidine) may make it worse.

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. 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. Noradrenaline and preferential serotonin-reuptake inhibitor (non selective monoamine reuptake inhibitors), ATC code: N06A A04.

Mechanism of action

The therapeutic activity of Anafranil is believed to be based on its ability to inhibit the neuronal re-uptake 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.

Anafranil also has a wide pharmacological spectrum of action, which includes alphal-adrenolytic, anticholinergic, antihistaminic, and antiserotonergic (5-HT-receptor blocking) properties.

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 "first-pass" metabolism to desmethylclomipramine (an active metabolite). The bioavailability of clomipramine is not markedly affected by the ingestion of food but the onset of absorption and therefore the time to peak may be delayed. Coated tablets and sustained release tablets are bioequivalent with respect to amount absorbed.

During oral administration of constant daily doses of Anafranil the steady state plasma concentrations of clomipramine and desmethylclomipramine (active metabolite) and the ratio between these concentrations show a high variability between patients, e.g. 75mg Anafranil daily produces steady state concentrations of clomipramine ranging from about 20 to 175ng/ml. Levels of desmethylclomipramine follow a similar pattern but are 40-85% higher.

Distribution:

Clomipramine is 97.6% bound to plasma proteins. The apparent volume of distribution is about 12-17 L/kg bodyweight. Concentrations in cerebrospinal fluid are about 2% of the plasma concentration.

Biotransformation:

The major route of transformation of clomipramine is demethylation to desmethylclomipramine. In addition, clomipramine and desmethylclomipramine are hydroxylated to 8-hydroxy-clomipramine and 8-hydroxy-desmethylclomipramine but little is known about their activity in vivo. The hydroxylation of clomipramine and desmethylclomipramine is
under genetic control similar to that of debrisoquine. In poor metabolisers of
debrisoquine this may lead to high concentrations of desmethylclomipramine;
concentrations of clomipramine are less significantly influenced.

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.

Characteristics in patients:
In elderly patients, plasma clomipramine concentrations may be higher for a
given dose than would be expected in younger patients because of reduced
metabolic clearance.

The effects of hepatic and renal impairment on the pharmacokinetics of
clomipramine have not been determined.

5.3 Preclinical safety data

Repeat-dose toxicity
Phospholipidosis and testicular changes considered to be secondary to the
phospholipidosis, commonly associated with tricyclic compounds, have
been observed with clomipramine hydrochloride at doses ≥4 fold greater
than the maximum recommended human daily dose (MRHD). The clinical
relevance of these findings is unknown.

Reproductive toxicity
Clomipramine hydrochloride demonstrated evidence of embryotoxicity e.g.
increased embryolethality and growth retardation, in the rat and mouse studies
(at doses which are 5 to 10 times the estimated oral MRHD of 5 mg/kg on a
mg/kg basis), but not in the rabbit study. The safety margin for increased
embryolethality based on the administered dose is 2.5 times the oral MHRD.

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
The administration of clomipramine hydrochloride to mice and rats for 104 weeks did not show any evidence of carcinogenicity at dose levels representing 16-20 times the estimated oral MRHD of 5 mg/kg on a mg/kg basis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose, gelatin (220 Bloom) and magnesium stearate, yellow iron oxide (E172), black iron oxide (E172), red iron oxide (E172), titanium dioxide and brown printing ink.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage

Store below 30°C. Store in the original container, in order to protect from moisture.

6.5 Nature and Contents of Container

The capsules are two tone light grey/caramel-coloured, hard gelatin size 4, imprinted ‘Geigy’ and come in PVC/PVDC/aluminium blister packs in pack sizes of 56 and 100.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER

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