

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו בדצמבר 2014

ANAFRANIL®

25 mg Coated tablets, 75 mg Slow-release tablets

Prescribing Information

1. Trade name

ANAFRANIL 25 mg coated tablets

ANAFRANIL 75 mg slow-release tablets

2. Description and composition

Pharmaceutical form

Coated tablets (Anafranil 25 mg)

Slow-release tablets, divisible (Anafranil SR 75 mg Divitabs)

Active substance

The active ingredient is 3-Chloro-5-[3-(dimethylamino)-propyl]10,11-dihydro-5H-dibenz-[b,f]azepine hydrochloride (clomipramine hydrochloride).

One coated tablet contains 25 mg clomipramine hydrochloride.

One slow-release tablet (divisible) contains 75 mg clomipramine hydrochloride.

Active moiety

Clomipramine

Excipients

25mg Coated tablets: lactose monohydrate, maize starch, silica colloidal anhydrous, stearic acid, talc, magnesium stearate, glycerol 85%, hydroxypropyl methylcellulose, vinylpyrrolidone/vinylacetate copolymer, titanium dioxide, sucrose cryst., polyvinylpyrrolidone K30, dispersed yellow 15093 instead 5% EEC172+95% EEC171, polyethylene glycol 8000, cellulose microcrystalline (avicel PH 101).

75mg Slow-release, divisible tablets: calcium hydrogen phosphate dihydrate, polyacrylate dispersion 30%, calcium stearate, silica collydalis anhydrica, hydroxypropyl methylcellulose, talc, titanium dioxide, polyoxyl 40 hydrogenated castor oil, red iron oxide.

3. Indications

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.

Obsessive-compulsive syndromes

No experience is available in children younger than 5 years of age.

4. Dosage and administration

Before initiating treatment with Anafranil, hypokalemia should be treated (see section 6 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 6 Warnings and precautions and 8 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 interchangeably in equivalent doses.

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

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. Start treatment with 10 mg daily. Gradually raise the dosage to an optimum level of 30-50 mg daily, which should be reached after about 10 days and then maintained until the end of treatment.

Children and Adolescents

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

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.

No experience is available in children under 5 years.

Renal impairment

Anafranil should be given with caution in patients with renal impairment (see section 6 Warnings and precautions and 11 Clinical pharmacology).

Hepatic impairment

Anafranil should be given with caution in patients with hepatic impairment (see section 6 Warnings and precautions and 11 Clinical pharmacology).

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 (see section 14 Pharmaceutical information).

Anafranil can be administered with or without food.

5. Contraindications

Known hypersensitivity to clomipramine or any of the excipients, or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group.

Anafranil must not be given in combination, or within 14 days before or after treatment, with a MAO inhibitor (see section 8 Interactions). The concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated.

Recent myocardial infarction.

Congenital long QT syndrome.

6. Warnings and precautions

Risk of suicide

Risk of suicide is inherent to severe depression and may persist until significant remission occurs. 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.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide.

Antidepressants increased the risk of suicidal thinking and behaviour (suicidality) in short-term studies in children, adolescents and young adults less than 25 years old with depressive disorders and other psychiatric disorders.

Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 25; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

All patients being treated with Anafranil for any indication should be observed closely for clinical worsening, suicidality and other psychiatric symptoms (see section 7 Adverse drug reactions), especially during the initial phase of therapy or at times of dose changes.

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 (see also Treatment discontinuation in section 6 Warnings and precautions).

Families and caregivers of both paediatric and adult patients being treated with antidepressants for both psychiatric and nonpsychiatric indications, should be alerted about the need to monitor patients for the emergence of other psychiatric symptoms (see section 7 Adverse drug reactions), 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 consistent with good patient management, in order to reduce the risk of overdose. Anafranil has been reported to be associated with fewer deaths following overdose than other tricyclic antidepressants.

Other psychiatric effects

Many patients with panic disorder experience more marked anxiety at the start of the treatment with Anafranil (see section 4 Dosage and administration). 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 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 (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 Dosage and administration and 8 Interactions). 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 sections 4 Dosage and administration and 8 Interactions).

Before starting treatment with Anafranil, 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 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, SNaRIs, tricyclic antidepressants or lithium (see sections 4 Dosage and administration and 8 Interactions). 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.

Like related tricyclic antidepressants, Anafranil 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 tumours 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 cardiac toxicity.

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. Tricyclic antidepressants 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.

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.

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 and during prolonged treatment.

Anaesthesia

Before general or local anaesthesia, the anaesthetist should be told that the patient has been receiving Anafranil (see section 8 Interactions).

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 certain symptoms (see section 7 Adverse drug reactions, for a description of the risks of discontinuation of Anafranil).

Lactose and sucrose

Anafranil coated tablets contain lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, severe lactase deficiency, sucrase-isomaltase insufficiency or glucose-galactose malabsorption should not take Anafranil coated tablets.

Driving and using machines

Patients receiving Anafranil should be warned that blurred vision, drowsiness and other nervous system and psychiatric related disorders such as somnolence, disturbance in attention, confusion, disorientation, aggravation of depression, delirium etc. (see section 7 Adverse drug reactions) 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 8 Interactions).

7. Adverse drug reactions

Summary of the safety profile

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 ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$) very rare ($< 1/10,000$), including isolated reports. The ADRs tabulated below are based on clinical trial results as well as post-marketing reports.

Table 7-1 Tabulated summary of adverse drug reactions

Blood and lymphatic system disorders	
Very rare	Leucopenia, agranulocytosis, thrombocytopenia, eosinophilia
Cardiac disorders	
Common	Sinus tachycardia, palpitation, 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	Accommodation disorder, vision blurred
Common	Mydriasis

Very rare	Glaucoma
Gastrointestinal disorders	
Very common	Nausea, dry mouth, constipation
Common	Vomiting, abdominal disorders, diarrhea
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
Metabolism and nutrition disorders	
Very common	Increased appetite
Common	Decreased appetite
Musculoskeletal and connective tissue disorders	
Common	Muscular weakness
Nervous system disorders	
Very common	Dizziness, tremor, headache, myoclonus, somnolence
Common	Speech disorder, paraesthesias, muscle 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
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 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

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 unknown: Serotonin syndrome, extrapyramidal symptoms (including akathisia and tardive dyskinesia).

Musculoskeletal and connective tissue disorders

Frequency unknown: Rhabdomyolysis (as a complication of neuroleptic malignant syndrome).

Investigations

Frequency unknown: Blood prolactin increased.

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 section 6 Warnings and precautions).

Bone fractures

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

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.

8. Interactions

Interactions resulting in a contraindication

MAO inhibitors

Do not give Anafranil for at least 2 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). MAO inhibitors, which are also potent CYP2D6 inhibitors *in vivo*, such as moclobemide, are contraindicated for coadministration with clomipramine (see section 5 Contraindications). The same applies when giving a MAO inhibitor after previous treatment

with Anafranil. In both instances Anafranil or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored (see section 5 Contraindications).

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 two-week washout period must be observed if the MAO-A inhibitor is given after Anafranil has been used.

Interactions resulting in a concomitant use not recommended

Antiarrhythmics

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 hypokalemia, which in turn increases the risk of QTc prolongation and torsades de pointes. Hypokalemia should therefore be treated prior to administration of Anafranil (see sections 4 Dosage and administration and 6 Warnings and precautions).

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 Dosage and administration and 6 Warnings and precautions.

Serotonergic agents

Serotonin Syndrome can possibly occur when clomipramine is administered with serotonergic co-medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenergic reuptake inhibitors (SNRIs), tricyclic antidepressants or lithium (see sections 4 Dosage and administration and 6 Warnings and precautions). 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

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

Coadministration of Anafranil with oral antifungal 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 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 may also 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

Anafranil may diminish or abolish the antihypertensive effects of adrenergic neuron blockers such as 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 sympathomimetics such as adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine (e.g. local anaesthetics).

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 plasma prothrombin 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 concentrations of co-administered compounds that are primarily cleared by CYP2D6 in extensive metabolizers.

9. Pregnancy and breast-feeding

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 active substance passes into the 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 13 Non clinical safety data).

No interaction between chronic oral contraceptive use (15 or 30 micrograms ethinyl estradiol daily) and Anafranil (25 mg daily) has been documented (see section 8 Interactions).

10. Overdosage

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.

Rare cases of pharmacobezoar, of varying severity including fatal outcome, have been reported in association with overdose of slow 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 Anafranil 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 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.

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-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

Drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity and choreoathetoid 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 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 symptoms is based on modern methods of intensive care, with continuous monitoring of cardiac function, blood gases, and electrolytes, and if necessary emergency measures such as anticonvulsive therapy, artificial respiration, and resuscitation.

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.

11. Clinical pharmacology

Pharmacodynamic properties (PD)

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 α_1 -adrenolytic, anticholinergic, antihistaminic, and antiserotonergic (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.

Anafranil also exerts a specific effect on obsessive-compulsive disorder distinct from its antidepressant effects.

Pharmacokinetic properties (PK)

Absorption

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

Following single dose administration 25 mg coated tablet and 75 mg slow 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 (T_{max} 9.00 ± 1.81 hr), respectively. The dose of 75 mg daily, administered either as coated tablets of 25 mg t.i.d. or as a slow-release tablet of 75 mg once daily, produces steady-state plasma concentrations ranging from about 20 to 175 ng/mL.

The steady-state plasma 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 of 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-hydroxyclopmipramine 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

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 faeces. 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.

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 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 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.

Slow release formulation

Slow release of clomipramine from Anafranil slow 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 slow release formulation, observed C_{max} 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 slow release formulation, C_{min} and C_{max} levels attained at steady state are within the therapeutic range. Slow-release tablets are bioequivalent with coated tablets and capsules.

12. Clinical studies

No recent clinical trials have been conducted with Anafranil.

13. Non-clinical 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.

14. Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

25mg Coated tablets: Store below 25°C, protect from moisture.

75mg Slow release tablets: Store below 25°C, protect from moisture.

Anafranil must be kept out of the reach and sight of children.

Instructions for use and handling

The slow-release tablets should be swallowed whole. The Divitabs (slow-release tablets divisible) can be halved, allowing the dosage to be adapted individually, but they should not be chewed.

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