NOVARTIS

Drug Regulatory Affairs

ANAFRANIL® (clomipramine)

25 mg / 2 mL solution for injection;
25 mg / 2 mL concentrate for solution for infusion

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

Author(s):	Dr. Renate Allan, Dr. Jürgen Gottowik, Dr. Dinah Blecher, Eric Randolph
GLC approval:	19-Jan-1995, amended 22-Aug-2001, 9-May-2003, 2-June-2005, 22-May-2007, 7-Jul-2009 and 15-Jun-2010
Release date:	23-Aug-2010
Tracking Number:	2010-PSB/GLC-0296-s
Document status:	Final
Number of pages:	

1 Name of the medicinal product

ANAFRANIL® 25 mg / 2 mL solution for injection; 25 mg / 2 mL concentrate for solution for infusion

2 Qualitative and quantitative composition

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

One ampoule contains 25 mg clomipramine hydrochloride in 2 mL aqueous solution.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Solution for injection; concentrate for solution for infusion (in ampoules).

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

Treatment of depressive states of varying aetiology and symptomatology [40,44], e.g.

- endogenous, reactive, neurotic, organic, masked, and involutional forms of depression,
- depression associated with schizophrenia and personality disorders,
- depressive syndromes due to presenility or senility, to chronic painful conditions, and to chronic somatic diseases [44],
- depressive mood disorders of a reactive, neurotic, or psychopathic nature [44].

Obsessive-compulsive syndromes.

Phobias [34-37,42,43,81,83,84].

Cataplexy accompanying narcolepsy [38,39].

Chronic painful conditions [47-49].

4.2 Posology and method of administration

Adults

Before initiating treatment with Anafranil, hypokalaemia should be treated (see 4.4 Special warnings and precautions for use) [150].

The dosage and method of administration 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, particularly in elderly patients or adolescents, who generally show a stronger response to Anafranil than patients of intermediate age groups.

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).

Intramuscular injection

Start with 1-2 ampoules of 25 mg, then increase the dosage by 1 ampoule daily until the patient is receiving 4-6 ampoules a day. Once there is an improvement in the patient's condition, gradually reduce the number of injections while switching the patient to oral maintenance therapy.

Intravenous infusion

Start with 2-3 ampoules (50-75 mg) once daily, diluted and mixed thoroughly with 250-500 mL isotonic saline or glucose solution and infused over a period of 1.5-3 hours. During the course of infusion patients should be carefully monitored for adverse effects. Particular attention should be paid to blood pressure, since postural hypotension may occur.

Once a distinct improvement is seen, the infusion treatment should be given for a further 3-5 days. To maintain the response, medication should then be continued by the oral route; 2 tablets of 25 mg are generally equivalent to 1 ampoule of 25 mg.

A gradual change-over from infusion treatment to oral maintenance therapy may also be achieved by switching first to intramuscular injections.

Children and adolescents

Not recommended for use in children and adolescents.

4.3 Contraindications

Known hypersensitivity to clomipramine or any of the excipients, or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group [91].

Anafranil should not be given in combination, or within 14 days before or after treatment, with a MAO inhibitor (see section 4.5 Interaction with other medicinal products and other forms of interaction) [92-94]. The concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated [132].

Recent myocardial infarction [14,41].

Congenital long QT syndrome [150].

4.4 Special warnings and precautions for use

Anaphylactic shock

Isolated cases of anaphylactic shock have been reported. Caution is called for when administering Anafranil i.v.

Risk of suicide

Risk of suicide is inherent to severe depression and may persist until significant remission occurs [96,123,124,139]. 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 less than 25 years old [173] with depressive disorders and other psychiatric disorders.

All patients being treated with Anafranil for any indication should be observed closely for clinical worsening, suicidality and other psychiatric symptoms (see section 4.8 Undesirable effects), 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 4.4 Special warnings and precautions for use).

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 4.8 Undesirable effects), as well as the emergence of suicidality, and to report such symptoms immediately to health care providers [170].

Anafranil has been reported to be associated with fewer deaths following overdose than other tricyclic antidepressants [123,141,142,149].

Other psychiatric effects

Many patients with panic disorder experience more marked anxiety at the start of the treatment with Anafranil. (see section 4.2 Posology and method of administration). This paradoxical initial increase in anxiety is most pronounced during the first few days of treatment and generally subsides within two weeks [90].

Activation of psychosis has occasionally been observed in patients with schizophrenia receiving tricyclic antidepressants [57,133].

Hypomanic or manic episodes have also been reported during a depressive phase in patients with cyclic affective disorders receiving treatment with a tricyclic antidepressant [102,103].

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 [57].

In predisposed and elderly patients, tricyclic antidepressants may provoke pharmacogenic (delirious) psychoses, particularly at night. These disappear within a few days of withdrawing the drug [57,92,107].

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 [41,97,98]. Monitoring of cardiac function and the ECG is indicated in such patients, as well as in elderly patients [14,40,71].

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 4.2 Posology and method of administration and 4.5 Interaction with other medicinal products and other forms of interaction). It is established that hypokalaemia is a risk-factor of QTc prolongation and torsades de pointes. Therefore, hypokalaemia should be treated before initiating treatment with Anafranil (see sections 4.2 Posology and method of administration and 4.5 Interaction with other medicinal products and other forms of interaction) [150].

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 [41].

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 4.2 Posology and method of administration and 4.5 Interaction 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 [167].

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) [17,57,95]. It appears that the occurrence of seizures is dose dependent [95]. 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 [14,106].

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) [14,99].

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 [92,100].

Specific treatment populations

Caution is called for when giving tricyclic antidepressants to patients with severe hepatic disease [14,29,100] and tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), in whom they may provoke hypertensive crises [69,70].

Caution is indicated in patients with hyperthyroidism or patients receiving thyroid preparations, owing to the possibility of cardiac toxicity [14].

In patients with liver disease, periodic monitoring of hepatic enzyme levels is recommended [92,100,104].

Caution is called for in patients with chronic constipation. Tricyclic antidepressants may cause paralytic ileus, particularly in elderly and in bedridden patients [100,108].

An increase in dental caries has been reported during long-term treatment with tricyclic antidepressants [55,56,100]. 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 [172].

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 [26,27,105].

Anaesthesia

Before general or local anaesthesia, the anaesthetist should be told that the patient has been receiving Anafranil (see section 4.5 Interaction with other medicinal products and other forms of interaction) [106].

Treatment discontinuation

Abrupt withdrawal should be avoided because of possible adverse reactions [109,110]. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see section 4.8 Undesirable effects, for a description of the risks of discontinuation of Anafranil [170]).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Adrenergic neuron blockers

Anafranil may diminish or abolish the antihypertensive effects of guanethidine, betanidine, reserpine, clonidine and alpha-methyldopa [92]. Patients requiring comedication for hypertension should therefore be given antihypertensives of a different type (e.g. vasodilators, or beta-blockers) [14,53].

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 [14,52,67].

CNS depressants

Tricyclic antidepressants may potentiate the effects of alcohol and other central depressant substances (e.g. barbiturates, benzodiazepines, or general anaesthetics) [52,92].

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 Posology and method of administration and 4.4 Special warnings and precautions for use) [150].

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) [93,111,132,167]. 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 4.3 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 [101,112].

Selective serotonin reuptake inhibitors (SSRI)

Comedication with SSRIs may lead to additive effects on the serotonergic system (see serotonergic agents) [115,116].

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 (SNaRIs), tricyclic antidepressants or 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 [167].

Sympathomimetic drugs

Anafranil may potentiate the cardiovascular effects of adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine (e.g. local anaesthetics) [52,53,73,113].

Pharmacokinetic interactions [166]

Anafranil (clomipramine) is predominately eliminated through metabolism [137]. The primary route of metabolism is demethylation to form the active metabolite, *N*-desmethylclomipramine, followed by hydroxylation and further conjugation of both *N*-desmethylclomipramine and the parent drug. Several cytochrome P450s are involved in the demethylation, mainly CYP3A4, CYP2C19, and CYP1A2 [151]. Elimination of both active components is by hydroxylation and this is catalyzed by CYP2D6 [151].

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 [152]. Concomitant administration of CYP1A2, CYP2C19 and CYP3A4 inhibitors are expected to increase clomipramine concentrations and decrease *N*-desmethylclomipramine, thus not necessarily affecting overall pharmacology.

- MAO inhibitors, which are also potent CYP2D6 inhibitors *in vivo*, such as moclobemide, are contraindicated for coadministration with clomipramine (see section 4.3 Contraindications) [166].
- Antiarrhythmics (such as quinidine and propafenone) which are potent inhibitors of CYP2D6, should not be used in combination with tricyclic antidepressants [67,114,153].
- SSRIs which are inhibitors of CYP2D6, such as fluoxetine, paroxetine, or sertraline [154], and of others including CYP1A2 and CYP2C19 (e.g. fluvoxamine), may also increase plasma concentrations of clomipramine, with corresponding adverse effects [115,116]. Steady-state serum levels of clomipramine increased ~4-fold by co-administration of fluvoxamine (*N*-desmethylclomipramine decreased ~2-fold) [155]. See sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use.
- Comedication of neuroleptics (e.g. phenothiazines) may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold, and seizures [92,117]. Combination with thioridazine may produce severe cardiac arrhythmias [118].
- 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 [174].
- Coadministration with the histamine$_2$ (H_2)-receptor antagonist, cimetidine (an inhibitor of several P450 enzymes, including CYP2D6 and CYP3A4), may increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced [52,58,156].
- No interaction between chronic oral contraceptive use (15 or 30 micrograms ethinyl estradiol daily) and Anafranil (25 mg daily) has been documented [157,160]. 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 [158,159,160], 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.
- Methylphenidate (e.g. Ritalin) may also increase concentrations of tricyclic antidepressants by potentially inhibiting their metabolism [14,52] and a dose reduction of the tricyclic antidepressant may be necessary.
- Some tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs, such as warfarin, and this may be through inhibition of their metabolism (CYP2C9) [92,119,161]. There is no evidence for the ability of clomipramine to inhibit the metabolism of anticoagulants, such as warfarin, however, careful monitoring of plasma prothrombin has been advised for this class of drug.

Concomitant administration of drugs known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19, and/or CYP1A2 may accelerate the metabolism and decrease the efficacy of Anafranil [52,73].

- CYP3A and CYP2C inducers, such as rifampicin or anticonvulsants (e.g. barbiturates, carbamazepine, phenobarbital and phenytoin), may decrease clomipramine concentrations.
- Known inducers of CYP1A2 (e.g. nicotine/components in cigarette smoke), decrease plasma concentrations of tricyclic drugs [14,157]. In cigarette smokers, clomipramine steady-state plasma concentrations were decreased 2-fold compared to non-smokers (no change in *N*-desmethylclomipramine) [157].

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 [162,163].

4.6 Pregnancy and lactation

Pregnancy

Experience with Anafranil in pregnancy is limited. Since there have been isolated reports of a possible connection between the use of tricyclic antidepressants and adverse effects (developmental disorders) on the foetus, treatment with Anafranil should be avoided during pregnancy, unless the anticipated benefits justify the potential risk to the fetus [61,64,65].

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 [59,60,134,168]. To avoid such symptoms, Anafranil should if possible be gradually withdrawn at least 7 weeks before the calculated date of confinement [66,148].

Lactation

Since the active substance passes into the breast milk, Anafranil should be gradually withdrawn or the infant weaned if the patient is breast-feeding [9,10].

4.7 Effects on ability to drive and use machines

Patients receiving Anafranil should be warned that blurred vision, drowsiness and other CNS symptoms (see section 4.8 Undesirable effects) may occur, in which case they should not drive, operate machinery, or do anything else requiring alertness [14,17,18,120]. 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

(including undesirable effects observed with oral dosage forms)

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.

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 [92,121].

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 (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports.

Central nervous system

Psychic effects

Very common: drowsiness, fatigue, restlessness, increased appetite [43,86,92,96].

Common: confusion, disorientation, hallucinations (particularly in elderly patients and patients with Parkinson's disease), anxiety states, agitation, sleep disturbances, mania, hypomania, aggressiveness, impaired memory, depersonalisation, aggravated depression, impaired concentration, insomnia, nightmares, yawning [16,86,87,92,96,107].

Uncommon: activation of psychotic symptoms [15,16,107].

Neurological effects

Very common: dizziness, tremor, headache, myoclonus [122].

Common: delirium, speech disorders, paraesthesias, muscle weakness, muscle hypertonia [88,92,122,125].

Uncommon: convulsions, ataxia [122].

Very rare: EEG changes, hyperpyrexia [14,17,18,126], neuroleptic malignant syndrome[171].

Anticholinergic effects

Very common: dry mouth, sweating, constipation, disorders of visual accommodation, blurred vision, disturbances of micturition [19,43,96].

Common: hot flushes, mydriasis [100].

Very rare: glaucoma, urinary retention [13,14,168].

Cardiovascular system

Common: sinus tachycardia, palpitations, postural hypotension, clinically irrelevant ECG changes (e.g. ST and T changes) in patients of normal cardiac status [92,96,127].

Uncommon: arrhythmias, increased blood pressure [92,127,128].

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) [14,19,20,97,150].

Gastrointestinal tract

Very common: nausea [96].

Common: vomiting, abdominal disorders, diarrhoea, anorexia [14,96].

Liver

Common: elevated transaminases [104].

Very rare: hepatitis with or without jaundice [28,104].

Skin

Common: allergic skin reactions (skin rash, urticaria), photosensitivity, pruritus [91].

Very rare: oedema (local or generalised), local reactions after intravenous use (thrombophlebitis, lymphangitis, burning sensation, allergic skin reactions), hair loss [14,19,138].

Endocrine system and metabolism

Very common: weight gain, disturbances of libido and potency [92,129].

Common: galactorrhoea, breast enlargement [92].

Very rare: SIADH (inappropriate antidiuretic hormone secretion syndrome) [21-25,92].

Hypersensitivity

Very rare: allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension [130,131].

Blood

Very rare: leucopenia, agranulocytosis, thrombocytopenia, eosinophilia, purpura [26,135].

Sense organs

Common: taste disturbances, tinnitus [86,96].

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 also section 4.4 Special warnings and precautions for use) [14,15,19,30,31].

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 [175].

4.9 Overdose

Overdose with ampoules has not been reported. The following information relates to overdose with oral dosage forms.

The signs and symptoms of overdose with Anafranil are similar to those reported with other tricyclic antidepressants. Cardiac abnormalities and neurological disturbances are the main complications. In children, accidental ingestion of any amount should be regarded as serious and potentially fatal.

Signs and symptoms [136]

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 [136].

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 [50,72]. In addition, symptoms consistent with Serotonin Syndrome (e.g. hyperpyrexia, myoclonus, delirium and coma) may be observed [167].

Cardiovascular system

Hypotension, tachycardia, arrhythmias, QTc prolongation and arrhythmias including torsades de pointes, conduction disorders, shock, heart failure; in very rare cases cardiac arrest [50,51,72,150].

Respiratory depression, cyanosis, vomiting, fever, mydriasis, sweating, and oliguria or anuria may also occur [51,72].

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 [51,72].

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 [50,51,72].

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. 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. Haemodialyses or peritoneal dialyses are ineffective because of the low plasma concentrations of clomipramine [51].

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 [32,33].

Anafranil also has a wide pharmacological spectrum of action, which includes alpha$_1$-adrenolytic, anticholinergic, antihistaminic, and antiserotonergic (5-HT-receptor blocking) properties [32,80].

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 [126].

In chronic pain with or without somatic causes, Anafranil acts presumably by facilitating serotonin and noradrenaline neurotransmission [143].

5.2 Pharmacokinetic properties

Absorption

Following repeated intramuscular or intravenous administration of 50-150 mg Anafranil daily, steady-state plasma concentrations are attained in the second week of treatment. These range from < 15 to 447 ng/mL for clomipramine and from < 15 to 669 ng/mL for *N*-desmethylclomipramine, which is also pharmacologically active [4].

Distribution

Clomipramine is 97.6% bound to plasma proteins [6]. The apparent distribution volume is about 12 to 17 L/kg bodyweight [2,145]. Concentrations in cerebrospinal fluid are about 2% of the plasma concentration [7]. Clomipramine passes into maternal milk in concentrations similar to those in plasma [9,10].

Biotransformation

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 [151,164,165,166]. Clomipramine and *N*-desmethylclomipramine are hydroxylated to form 8-hydroxyclomipramine or 8-hydroxy-*N*-desmethylclomipramine. The activity of the

8-hydroxy metabolites are not defined in vivo [137]. 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 [152,165]. Elimination of the active components, clomipramine and *N*-desmethylclomipramine, by formation of 2- and 8-hydroxy clomipramine is catalysed by CYP2D6 [151].

Elimination

After i.m. and i.v. administration, clomipramine is eliminated from plasma with a mean terminal half-life of 25 h (range 20-40 h) and 18 h, respectively [2,145].

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 [1,8]. The quantity of unchanged clomipramine and *N*-desmethylclomipramine excreted in the urine is about 2% and 0.5% of the dose administered, respectively [1,8].

Characteristics in patients

In elderly patients, owing to reduced metabolic clearance, plasma clomipramine concentrations at any given dose are higher than in younger patients [137,147]. The effects of hepatic and renal impairment on the pharmacokinetics of clomipramine have not been determined.

5.3 Preclinical safety data

According to the experimental data available, Anafranil has no mutagenic, carcinogenic, or teratogenic effects [75-79].

6 Pharmaceutical particulars

6.1 List of excipients

Glycerol, Water for injection.

Information might differ in some countries.

6.2 Incompatibilities

Known incompatibility: injectable solution of Anafranil with injectable solution of Voltaren® (diclofenac).

6.3 Shelf life

Five years.

Information might differ in some countries.

6.4 Special precautions for storage

Protect the ampoules from light.

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

Information might differ in some countries.

6.5 Nature and contents of container

Country-specific.

6.6 Instructions for use and handling

See section 4.2 Posology and method of administration.

This is a non-referenced document.