NOVARTIS

Anafranil®

Composition

Active substance(s)
Clomipramine hydrochloride

Excipients
Coated tablets
Tableting excipients

Sustained-release "Dictabs"
Tableting excipients.

Ampoules
Glycerol, water for injections to 2 ml.

Pharmaceutical form and quantity of active substance per unit

Coated tablets containing 10 or 25 mg clomipramine hydrochloride
Sustained-release "Dictabs" containing 75 mg clomipramine hydrochloride.
Ampoules containing 25 mg clomipramine hydrochloride per 2 ml

Indications / Potential uses

Indications
Treatment of depressive state of varying aetiology and symptomatology
- Endogenous, reactive, neurotic, organic, masked and involutional depression
- Depression associated with schizophrenia and psychopathy
- Depressive syndromes due to presenility or senility, chronic pain, chronic pain and chronic somatic diseases.
- Depressive mood disorders of a reactive, neurotic or psychopathic nature

Additional uses
- Phobias and panic attacks
- Obsessive-compulsive syndromes
- Catapleksy accompanying narcolepsy
- Chronic painful conditions (in particular cancer pain, neuropathic pain and idiopathic pain syndrome)

Children and adolescents
Obsessive-compulsive syndromes
Nocturnal enuresis in patients 6 years of age and older, once organic causes have been ruled out. Cautious assessment of benefits and risks. Potential alternative therapies should be considered. No data are available in children under 5 years of age.
Note: There is no pharmacological data on the efficacy of Anafranil in the treatment of children and adolescents with depressive states of varying aetiology, phobias, panic attacks, catapleksy accompanying narcolepsy and chronic painful conditions. Therefore, Anafranil should not be used in these indications in children and adolescents under 18 years of age.

Dosage and Administration

Before initiating treatment with Anafranil, hypokalaemia – if present – must be treated (see **Warnings and Precautions**).
The dosage and method of administration should be determined individually and adapted to the patient's condition. The aim is to achieve an optimum effect while keeping doses as low as possible and increasing them cautiously, particularly in elderly patients and patients with a history of epilepsy. Monitor response to Anafranil than patients in the intervening age groups.

The sustained-release tablets may be halved, but should not be chewed. They are divisible into two equal halves, enabling the dosage to be closely adapted to the patient's individual requirements.
As a precaution against possible QT prolongation and ventricular toxicity, the recommended doses of Anafranil should not be exceeded. Any increase in the dose of Anafranil should be made with caution if other serotonergic agents or medicinal products that prolong the QT interval are coadministered (see **Warnings and Precautions** and **Interactions**).

Depression, obsessive-compulsive syndromes, and phobias
Oral forms
Start treatment with one 25 mg tablet 2–3 times daily or one 75 mg sustained-release tablet once daily (preferably in the evening).
Increase dispense during the first week of treatment to e.g. by 25 mg every few days, depending on tolerability) to 4–6 tablets of 25 mg, or two 75 mg sustained-release tablets, daily. In severe cases the dose may be increased to a maximum of 250 mg daily.
Once there is a distinct improvement reduce to a maintenance dose of about 2–4 tablets of 25 mg, or one 75 mg sustained-release tablet, daily.

Intramuscular injection
Start with 1–2 ampoules of 25 mg, then increase by one ampoule daily until the patient is receiving 4–6 ampoules a day. Once there is an improvement, gradually reduce the number of injections while at the same time switching to oral therapy (maintenance dose).

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. Close monitoring for adverse effects is required during the infusion. Particular attention should be paid to blood pressure due to the risk of orthostatic hypotension.
Once there is a distinct improvement (normally within one week) subcutaneous infusion should be continued for a further 3–5 days. The patient should then be switched to oral maintenance therapy. As a general rule, two 25 mg tablets should replace one 25 mg ampoule.
A gradual switch from infusion treatment to oral maintenance therapy may also be achieved by switching first to intramuscular injections.
Anafranil ampoules are not suitable for paediatric use.

Panic attacks, agoraphobia
Start with one 10 mg tablet daily. Depending on tolerability, increase the dosage until the desired response is obtained. The required daily dosage varies considerably from patient to patient within the range 25–100 mg, but as much as 150 mg may be given if necessary. It is recommended that treatment be given for at least six months and that the maintenance dose be gradually reduced during this time.

Catapleksy accompanying narcolepsy
As oral dose of 25–75 mg/day

Chronic painful conditions
The dosage must be individualized in patients with chronic painful conditions (10-150 mg/day), taking into account (and, as appropriate, reducing the dose off) any concomitant analgesic medications.

Elderly patients
Start treatment with one 10 mg tablet daily. Gradually increase the dosage to an optimum level of 30–50 mg daily, which should be reached after about 10 days. The optimum daily dosage is maintained until the end of treatment.

Children and adolescents
Obsessive-compulsive syndromes
As in adults, the starting dose is 25 mg per day. During the first 2 weeks, the dose should be divided into several sub-doses, as appropriate, and – depending on tolerability – should gradually be increased to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may gradually be increased in the following weeks to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller.

Nocturnal enuresis (only in children aged 6 years or older)
Initial daily dose
Children 6-8 years of age
2–3 tablets of 10 mg

Children 9-12 years of age
1-2 tablets of 25 mg

Children over 12 years of age
1-3 tablets of 25 mg

The higher doses are for patients who do not respond fully to treatment within one week, and should not be exceeded.
Treatment (including time needed for gradual withdrawal) should not be given for more than three months.
The tablets should be given in a single dose after the evening meal, but children who wet the bed early in the night should be given part of the dose earlier, at 16:00 (4 p.m.).
Before starting treatment in children/adolescents, particular attention must be paid to warnings and precautions relating to the risk of suicide (see **Warnings and Precautions**).
No data are available on the treatment of children under 6 years of age.

Contraindications

Hypersensitivity to clomipramine or any of the excipients, or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group.
Antiarrhythmics such as quinidine and propafenone, which are potent inhibitors of CYP2D6, must not be used in combination with tricyclic antidepressants.
Anafranil must not be given in combination with, or within 14 days before or after an MAO inhibitor (see **Interactions**). Concomitant use of a tricyclic antidepressant and reversible MAO-A inhibitor such as moclobemide is also contraindicated.
Use is also contraindicated in patients with recent myocardial infarction or congenital long QT syndrome.
Anafranil should not be administered in patients with:
- acute intoxication with CNS depressants (such as hypnotics, analgesics or psychotropic agents) or alcohol
- acute alcohol intoxication
- acute delirium
- untreated narrow-angle glaucoma
- prostatic hypertrophy with urinary retention
- pyloric stenosis
- paralytic ileus

Warnings and Precautions

Risk of suicide
Depression is associated with an elevated risk of suicidal ideation, self-mutilation and completed suicide. Suicidal ideation and suicidal behaviour may also be exacerbated in patients undergoing antidepressant treatment.
Anafranil should not be used to treat depression in children and adolescents under 18 years of age. Although an association of depression in this age group, tricyclic antidepressants showed no therapeutic efficacy.
Based on data from published studies with selective serotonin reuptake inhibitors (SSRIs) and comparable products, there is an elevated risk of suicide when treating depression in children and adolescents. A similar effect can not be ruled out for other antidepressants (including Anafranil), for which such data are not available.

Patients undergoing treatment with antidepressants must therefore be closely monitored for signs of worsening depression, in particular suicidal behaviour, restlessness and/or akathisia (inner restlessness, psychomotor agitation), above all at the start of treatment and when the dosage is changed. Patients must also be closely monitored after treatment ends because such symptoms may occur as signs of withdrawal or recipient relapse.
Psychiatric emergencies and/or worsening symptoms may also be associated with an elevated risk of suicidal behaviour, and the same precautions must therefore be observed as in the treatment of depression. Families and caregivers of patients should be told to be alert to the emergence of other psychiatric symptoms (see **Adverse effects**) and suicidality, and to report them immediately to the attending physician.
Clomipramine hydrochloride is not a suitable means of avoiding the hospitalization required in cases of self-endangerment. Doctors should prescribe the smallest suitable pack size (if the medicinal product, particularly at the start of treatment, in order to reduce the risk of self-endangerment.
As regards the risk of fatal overdose, fewer deaths have been reported with Anafranil than with other tricyclic antidepressants. To reduce the risk of overdose, Anafranil should be prescribed at the lowest possible dose consistent with optimum patient management.

Other psychiatric effects
Many patients with panic attacks experience more marked anxiety at the start of Anafranil therapy. 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 schizophrenic patients receiving tricyclic antidepressants. As a result, such patients should be closely monitored for signs of worsening paranoia and excitation in patients with agitation or concomitant schizophrenic symptoms.
Hypomanic and manic episodes have been reported during depressive phases in patients with bipolar affective disorders receiving treatment with tricyclic antidepressants. In such cases it may be necessary to reduce the dosage of, or withdraw, Anafranil and adjust the patient's medication. If a manic phase is not controlled, low dose therapy with Anafranil may be resumed if required.
In predisposed and elderly patients, tricyclic antidepressants may provoke pharmacogenic (delirious) psychoses, particularly at night. These disappear without specific treatment within a few days of withdrawing the drug.

Convulsions
Tricyclic antidepressants lower the seizure threshold and Anafranil must therefore be used with extreme caution in patients with epilepsy or other predisposing factors. In the presence of such risk factors, concomitant use of neuroleptics, withdrawal of alcohol or of drugs with anticonvulsant properties such as benzodiazepines). The occurrence of seizures seems to be dose-dependent. The recommended total daily dose must therefore not be exceeded.
Patients should be kept under close supervision when tricyclic antidepressants are given in conjunction with electroconvulsive therapy.

Anticholinergic effects
Because of its anticholinergic properties, Anafranil must be used with caution in patients with urinary retention, raised intraocular pressure, narrow angle glaucoma, or urinary retention (e.g. due to prostate disease).
Both decreased lacrimation and accumulation of mucoid secretions – caused by the anticholinergic properties of tricyclic antidepressants – may lead to damage to the corneal epithelium in patients who wear contact lenses.

Serotonin syndrome
Due to the risk of serotonergic toxicity, it is advisable to adhere to the recommended dose. Serotonin syndrome, with symptoms such as hyperpyrexia, myoclonus, agitation, epileptic seizures, tachycardia and coma, may occur when Anafranil is administered combined with serotonergic medications such as SSRIs, SNRIs, tricyclic antidepressants or lithium (see **Dosage and Administration** and **Interactions**). A washout period of two to three weeks is advised before and after treatment with fluoxetine.

Cardiovascular disorders
Particular caution is called for in patients with cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders (e.g. grade I-III atrioventricular block) or arrhythmias. Monitoring of cardiac function and the ECG is indicated in such patients, as well as in elderly patients.
Tricyclic drugs, like other antidepressant and atypical vertricular tachycardia when doses or plasma concentrations of clomipramine are elevated, as occurs during comedication with selective serotonin reuptake inhibitors (SSRIs) or serotonin-noradrenaline reuptake inhibitors (SNRIs; see **Interactions**). Therefore, concomitant administration of drugs that can cause accumulation of clomipramine should be avoided. Equally, concomitant administration of drugs that prolong the QT interval should be avoided.
Hypokalaemia is a known risk factor for QTc prolongation and torsade de pointes, and should therefore be treated before initiating Anafranil therapy. Caution is required when using Anafranil in combination with SSRIs, SNRIs or diuretics (see **Interactions**).
Before starting treatment it is advisable to check the patient's blood pressure because of the possibility of a drop in blood pressure in patients with hypotension or circulatory instability.

Specific patient populations and long-term therapy
Caution is advised when prescribing tricyclic antidepressants to elderly patients or patients with prostatic hypertrophy and glaucoma, particularly in elderly and bedridden patients.
Regular monitoring of liver enzyme values is recommended in patients with liver disease.
Caution is required when giving tricyclic antidepressants to patients with severe liver disease or tumours of the adrenal medulla (e.g. phaeochromocytoma or neuroblastoma) because of the risk of precipitating hypertensive crisis.
Caution is indicated in patients with hyperthyroidism and patients receiving thyroid preparations, since the anticholinergic action of the drug is likely to increase the overall risk of unwanted cardiac effects.
Increases in dental caries and oral mucosal changes have been observed in long-term treatment with tricyclic antidepressants. Regular dental check-ups are therefore advisable during long-term treatment.
No long-term safety data are available on growth, maturation and cognitive and behavioural development in children and adolescents.

Hypersensitivity reactions
There have been isolated reports of anaphylactic shock. Caution is required when administering Anafranil intravenously.

White blood cell count
Although there have been only isolated reports of WBC count changes during treatment with Anafranil, periodic blood cell counts are recommended in patients at risk of blood dyscrasia. Such tests are indicated, particularly during the first few months of therapy and during prolonged treatment. Anafranil must be withdrawn if the neutrophil count falls to a pathological level.

Anaesthesia
Prior to general or local anaesthesia, the anaesthetist must be informed that the patient is receiving treatment with Anafranil.

Other
Hyperthermia (a symptom of neuroleptic malignant syndrome) has been reported in some patients receiving concomitant treatment with Anafranil and a neuroleptic agent.

Discontinuation of treatment
Abrupt withdrawal should be avoided because of possible adverse effects. If treatment has to be discontinued, the dose should be tapered off as rapidly as possible, but always bearing in mind that abrupt withdrawal may be associated with certain symptoms (see **Adverse effects**).

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

Interactions

Pharmacodynamic interactions
Monoamine oxidase (MAO) inhibitors
Anafranil must not be given for at least two weeks following discontinuation of treatment with an MAO inhibitor due to the risk of severe symptoms such as hypertensive crisis, hyperpyrexia, and symptoms associated with serotonin syndrome, such as myoclonus, agitation, convulsions, delirium and coma. The same applies if an MAO inhibitor is to be given after discontinuation of Anafranil. In both instances Anafranil or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored (see **Contraindications**).
There is evidence to suggest that Anafranil may be given as early as 24 hours after a reversible MAO-A inhibitor such as moclobemide, but the two-week washout period absolutely must be observed if the MAO-A inhibitor is given after previous treatment with Anafranil.

Selective serotonin reuptake inhibitors (SSRIs)
Concomitant use of Anafranil and SSRIs may result in an additive effect on the serotonergic system.

Serotonergic agents
Serotonin syndrome may occur when clomipramine is coadministered with serotonergic medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants or lithium (see **Dosage and Administration** and **Warnings and Precautions**). A washout period of two to three weeks is advised before and after treatment with fluoxetine.

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

Sympathomimetics
Anafranil may increase the cardiovascular effects of adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine (e.g. in local anaesthetics).

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

Anticholinergic agents
Tricyclic antidepressants may potentiate the effects of these drugs (e.g. phenothiazine, antiparkinsonian agents, antihistamines, atropine and biperidoxil on the eyes, CNS, intestine and bladder. There is also a risk of hyperthermia.

Diuretics
Comedication with diuretics may lead to hypokalaemia, which in turn increases the risk of QTc prolongation and torsade de pointes. Hypokalaemia in particular should therefore be treated prior to administration of Anafranil.
Care is also necessary to correct other possible electrolyte disorders, in particular hypomagnesaemia, prior to initiating treatment with Anafranil.

Pharmacokinetic interactions
Anafranil (clomipramine) is predominately eliminated through metabolism. The primary route of metabolism is demethylation to form the active metabolite, N-desmethylclomipramine, followed by hydroxylation and further conjugation of both N-desmethylclomipramine and the parent drug. Several cytochrome P450s are involved in the demethylation, mainly CYP2A6, CYP2C19 and CYP1A2. Elimination of both active components is by hydroxylation catalysed by CYP2D6.
Concomitant administration of CYP2D6 inhibitors may lead to as much as an approximately 3-fold increase in the concentration of both active components in patients with a deficiency in hydroxylation of debrisoquine (poor metabolizers, PM) relative to extensive metabolizer phenotype. Concomitant administration of CYP1A2, CYP2C19 and CYP3A4 inhibitors can be expected to increase concentrations of clomipramine and decrease concentrations of N-desmethylclomipramine, thus not necessarily affecting the overall pharmacodynamic.
- MAO inhibitors such as moclobemide, which are also potent inhibitors of CYP2D6, must not be coadministered with clomipramine (see **Contraindications**).
Antiarrhythmics such as quinidine and propafenone, which are potent inhibitors of CYP2D6, must not be used in combination with tricyclic antidepressants.
- Fluvoxamine, fluoxetine, paroxetine, or sertraline, which are inhibitors of CYP2D6, and SSRIs such as fluoxamine, which inhibit other CYP enzymes – including CYP1A2 and CYP2C19 – may also increase plasma concentrations of clomipramine, with corresponding adverse effects. Steady-state serum levels of clomipramine increased approximately 4-fold following coadministration of fluoxamine, while N-desmethylclomipramine levels rose approximately 2-fold (see **Dosage and Administration** and **Warnings and Precautions**).
Co-medication with neuroleptics, e.g. phenothiazines, may result in increased plasma levels of tricyclic antidepressants, a lowered epileptic convulsion threshold, and seizures. Combination with thioridazine may precipitate severe cardiac arrhythmia.
Combination with the histamine H2-receptor antagonist, cimetidine, which inhibits CYP2D6, CYP1A2, CYP2C19 and CYP3A4, may increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.
No interaction has been demonstrated between 25 mg Anafranil daily and long-term oral contraceptive use (15 or 30 µg ethinylestradiol daily). Oestrogens are not known to be inhibitors of CYP2D6, the major enzyme involved in clomipramine clearance; therefore, interaction is unlikely. However, there is the possibility of increased imipramine bioavailability, greater therapeutic efficacy and more frequent adverse effects in patients given high doses of oestrogen (50 µg daily) concomitantly with the tricyclic antidepressant imipramine, but the relevance of these cases for clomipramine and lower-dosed oestrogen is unclear. Monitoring the therapeutic response to tricyclic antidepressants is recommended and the dosage of oestrogen (50 µg daily) are given, and dose adjustments may be necessary.
Methylphenidate, e.g. Ritalin®, may also increase concentrations of tricyclic antidepressants by inhibiting their metabolism; a dose reduction of the tricyclic antidepressant may become necessary.
Some tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs, such as warfarin, possibly by inhibiting CYP2C9 metabolism. There is no evidence that clomipramine inhibits the metabolism of anticoagulants such as warfarin, but close monitoring of plasma prothrombin has been advised for this drug class. Concomitant administration of substances that induce cytochrome P450 enzymes (in particular CYP3A4, CYP2C19 and/or CYP1A2) may accelerate clomipramine metabolism and decrease its plasma levels. Caution is advised.
- Inducers of CYP1A4 and CYP2C19, such as rifampicin or anticonvulsants (e.g. barbiturates, carbamazepine, phenobarbital and phenytoin) may lower plasma levels of clomipramine.
- Inducers of CYP1A2 (e.g. nicotine / components of cigarette smoke) lower plasma levels of tricyclic antidepressants. Steady state plasma levels in cigarette smokers were half those in non-smokers (no change in plasma levels of N-desmethylclomipramine).
- Clomipramine is also an in vitro (Ki = 2.2 µM) and in vivo inhibitor of CYP2D6 activity (sparteine oxidation), and may therefore cause a rise in levels of concurrently administered substances that are predominantly metabolized by CYP2D6 in extensive metabolizers.

Pregnancy and Lactation

Pregnancy
There is definite evidence of risk to the human fetus, but this may be outweighed by the therapeutic benefit for the mother. There have been isolated reports of a possible connection between the use of tricyclic antidepressants and adverse effects on the fetus (developmental disturbances); treatment with Anafranil should therefore be avoided during pregnancy, and should only be considered if absolutely essential and if there is no alternative (non-risk drug).
Infants born to mothers who had taken tricyclic antidepressants right up until the birth showed symptoms such as respiratory disorders, lethargy, colic, irritability, hypotension or hypertension, muscle hypertonia, tremor and epileptic seizures during the first few hours or days after birth.
In order to avoid such symptoms, Anafranil should be withdrawn at least 2 weeks before the estimated date of delivery, if medically justified.

Lactation
The active substance is excreted in breast milk and the infant should therefore be weaned or the drug gradually withdrawn.

Effects on ability to drive and use machines

Patients receiving Anafranil should be warned that blurred vision, light-headedness and other CNS symptoms (see **Adverse effects**) may occur, in which case they should not drive, use machines or do anything else requiring complete alertness. Patients should also be warned that these effects may be potentiated by alcohol and by other medicinal products (see **Interactions**).

Adverse effects

Most adverse effects are usually transient, disappearing as treatment continues or following dose reduction. They do not always correlate with plasma drug levels or dose. It is often difficult to distinguish certain adverse effects from symptoms of depression, e.g. fatigue, sleep disturbance, agitation, anxiety, constipation and loss of libido.
If severe neurological or mental adverse effects occur, Anafranil should be withdrawn.
Elderly patients are particularly susceptible to anticholinergic, neurological, mental and cardiovascular effects. Their ability to tolerate psychotropic drugs may be reduced, leading to a risk of elevated plasma levels even at therapeutic doses.

Frequencies
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000), including isolated post-marketing reports (< 1/10 000).

Blood and lymphatic system disorders
Very rare: Leucopenia, agranulocytosis, thrombocytopenia, eosinophilia and purpura.

Immune system disorders
Very rare: Allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension.

Endocrine disorders
Very common: Dry mouth, sweating, disturbances of micturition
Common: Hot flushes, mydriasis.
Very rare: SIADH (syndrome of inappropriate antidiuretic hormone secretion).

Metabolism and nutrition disorders
Very common: Weight gain.

Psychiatric disorders
Very common: Light-headedness, transient fatigue, restlessness, increased appetite.
Common: Confusion accompanied by disorientation and hallucinations (particularly in geriatric and parkinsonian patients), anxiety, excitation, sleep disturbance, mania, hypomania, aggressiveness, impairment of memory, yawning, personality changes, insomnia, nightmares, impairment of concentration, impairment of concentration.
Uncommon: Activation of psychotic symptoms.

Nervous system disorders
Very common: Dizziness, tremor, headache, myoclonus.
Common: Delirium, speech disturbance, paraesthesias, muscle weakness, muscle hypertonia.
Uncommon: Seizures, ataxia.
Very rare: EEG changes, hyperpyrexia, extrapyramidal symptoms (including tardive dyskinesia), drug fever, neuroleptic malignant syndrome.

Eye disorders
Common: Blurred vision, Accommodation disorders, blurred vision.
Very rare: Glaucoma.

Ear and labyrinth disorders
Common: Tinnitus.

Cardiac disorders
Common: Sinus tachycardia, palpitations and clinically irrelevant ECG changes (e.g. T and ST changes) in patients with normal cardiac status.
Uncommon: Arrhythmias, increased blood pressure.
Very rare: Conduction disturbances (e.g. widening of QRS complex, prolonged QT interval, PQ changes, bundle-branch block), torsade de pointes in hypokalaemia.

Vascular disorders
Common: Orthostatic hypotension.

Gastrointestinal disorders
Very common: Constipation.
Common: Nausea
Uncommon: Vomiting, abdominal disorders, diarrhoea, loss of appetite, dyspepsia.

Hepatobiliary disorders
Common: Elevated transaminases.
Very rare: Hepatitis with or without jaundice.

Skin disorders
Common: Allergic skin reactions (exanthema, urticaria), photosensitivity, pruritus.
Very rare: Local reactions following i.v. administration (thrombosis, thrombophlebitis, sensations of burning and allergic skin reactions), oedema (local or generalized), hair loss.

Renal and urinary disorders
Very rare: Water retention.

Reproductive system and breast disorders
Common: Dysfunctions of libido and potency.
Uncommon: Galactorrhoea, breast enlargement.

General disorders
The following symptoms occur uncommonly following abrupt treatment withdrawal or dose reduction: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, anxiety (see **Warnings and Precautions**).

Overdose

The initial signs and symptoms of Anafranil overdosage are similar to those reported with other tricyclic antidepressants. The main complications are cardiac abnormalities and disturbances of neurological function. In children, accidental ingestion of any amount of Anafranil must be regarded as serious and potentially fatal.
Symptoms generally appear within 4 hours of ingestion, with maximum severity after 24 hours. However, coma, fits and other adverse effects may be delayed. The clinical response usually sets in after 2–3 weeks of treatment.

In addition to its antidepressant effects Anafranil also exerts a specific effect in obsessive-compulsive disorders.
In chronic pain (with or without somatic causes) Anafranil presumably acts by facilitating serotonin and noradrenaline neurotransmission.

Pharmacokinetics

Absorption
Clomipramine is completely absorbed following both oral administration and intramuscular injection.
The systemic bioavailability of unchanged clomipramine is reduced by about 50% due to hepatic first-pass metabolism to the active metabolite, N-desmethylclomipramine. Ingestion of food has no marked effect on clomipramine bioavailability. It is only the onset of action of the drug that may be slightly delayed, due to increasing the time to peak absorption. Anafranil coated tablets and sustained-release tablets are bioequivalent with respect to the amount absorbed.
Oral administration of fixed daily doses is associated with considerable variation in steady-state plasma concentrations of unchanged clomipramine. A daily dose of 75 mg, administered either as one 25 mg tablet three times daily or as one 75 mg sustained-release tablet per day, produces steady-state plasma concentrations ranging from 20 to 175 ng/ml.
Steady-state concentrations of the active metabolite desmethylclomipramine follow a similar pattern. However, at a dosage of 75 mg daily, levels are 2 to 5 times higher than those of clomipramine.
Following repeated intravenous or intramuscular administration of 50-150 mg/day, steady-state plasma concentrations are attained during the second week of treatment. These range on average from < 15 to 443 ng/ml for unchanged clomipramine and from <15 to 669 ng/ml for desmethylclomipramine.

Distribution
Clomipramine is 97.6% bound to plasma proteins. The apparent distribution volume is about 12–17 litres/kg body weight. Concentration in the cerebrospinal fluid is approximately 2% of the plasma concentration. Clomipramine is excreted in breast milk at concentrations similar to those found in the plasma.

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, primarily CYP3A4, CYP2C19 and CYP1A2. In addition, clomipramine and N-desmethylclomipramine are hydroxylated to 8-hydroxy-clomipramine and 8-hydroxy-desmethylclomipramine, the activity of which remains largely unknown. 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.
CYP2D6 catalyses the elimination of the active components, clomipramine and N-desmethylclomipramine, by formation of 2- and 8-hydroxy clomipramine. The hydroxylation of clomipramine and desmethylclomipramine is under genetic control similar to that of debrisoquine. In poor metabolizers of debrisoquine this may lead to high concentrations of desmethylclomipramine, while concentrations of clomipramine are less influenced.

Elimination
Clomipramine is eliminated from the blood with a mean half-life of 21 hours (range, 12–36 hours); desmethylclomipramine with a mean half-life of 74 hours.
After i.m. and i.v. administration, clomipramine is eliminated from the plasma with a mean terminal half-life of 25 hours (range: 20–40 hours) and 18 hours, respectively.
About two-thirds of a single dose of clomipramine is excreted in the form of water-soluble conjugates in the urine, while approximately one-third is excreted in the faeces. Urinary excretion of unchanged clomipramine and desmethylclomipramine is about 2% and 0.5%, respectively.

Pharmacokinetics in special patient populations
Elderly patients
Irrespective of the dose administered, plasma concentrations of clomipramine are higher in elderly patients than in younger ones owing to reduced metabolic clearance.

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

Preclinical data

Hypermelanogenesis, lenticular calcification and atrophy, changes in the liver (vacuole formation and fatty infiltration, inflammation, hypertrophy), phospholipid deposits in the lungs, and arteriosclerotic changes in the lungs and testes have been observed in chronic toxicity studies.
The mutagenicity of clomipramine has not been adequately studied. In the Ames test, clomipramine showed no mutagenicity, but a mutagenic effect in studies in Drosophila. The relevance of these findings to clinical use is currently unknown. A 2-year, long-term study in rats yielded no evidence that clomipramine was carcinogenic. No teratogenicity was observed in reproductive toxicity studies in animals. Clomipramine, when administered prenatally and during the lactation phase, may cause behavioural disorders in the offspring.

Other information

Incompatibilities
Incompatibilities observed to date: Anafranil solution for injection/infusion and barbiturate sodium are incompatible.
Anafranil should not be mixed with other drugs.

Shelf-life
Do not use after the expiry date (= EXP) printed on the pack.
Once opened, the ampoules should be used immediately and not returned to storage.

Special precautions for storage
See folding box.

Pack sizes
Country specific pack sizes

Manufacturer
See folding box

Information last revised
May 2009

Approval date (text)
3 July 2009

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists
Arabic - 2009/4/10