NOVARTIS

## Anafranil®

Tricyclic antidepressant. Noradrenaline and preferential serotonin-reuptake inhibitor (nonselective monoamine reuptake inhibitors).

## DESCRIPTION AND COMPOSITION

### Pharmaceutical forms

Coated tablets (Anafranil 10mg, Anafranil 25mg)

Sustained-release tablets (Anafranil SR 75mg)

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

Capsules

Information might differ in some countries.

### 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 10 mg or 25 mg of clomipramine hydrochloride.

One sustained-release tablet (divisible and non-divisible) contains 75 mg clomipramine hydrochloride.

One capsule contains 10 mg, 25 mg or 50 mg clomipramine hydrochloride.

### Active moiety

Clomipramine

Certain dosage strengths and dosage forms may not be available in all countries.

## Excipients

10 mg and 25 mg Coated tablets: Lactose monohydrate, Maize starch, Hypromellose (hydroxypropyl methylcellulose), Magnesium stearate, Silica colloidal anhydrous, Talc, Copovidone (vinylpyrrolidone/vinylacetate copolymer), Titanium dioxide (E171), Sucrose, Povidone (polyvinylpyrrolidone), Iron oxide, yellow (E172), macrogol 8000 (polyethylene glycol 8000), Cellulose microcrystalline.

The 25 mg Coated tablets also contain Stearic acid and Glycerol (85%).

Sustained-release, divisible tablets: Calcium hydrogen phosphate dihydrate, Polyacrylate dispersion 30%, Calcium stearate, Silica colloidal anhydrous, Hypromellose (hydroxypropyl methylcellulose), Talc, Titanium dioxide, Macrogolglycerol hydroxystearate (polyoxyl 40 hydrogenated castor oil), Iron oxide red.

Sustained-release tablets (non-divisible) and capsules: excipients country-specific.

Pharmaceutical formulations may vary between countries.

## INDICATIONS

### Adults

Treatment of depressive states of varying aetiology and symptomatology, 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, depressive mood disorders of a reactive, neurotic, or psychopathic nature.

Obsessive-compulsive syndromes.

Phobias and panic attacks.

Cataplexy accompanying narcolepsy.

Chronic painful conditions.

### Children and adolescents

Obsessive-compulsive syndromes.

Nocturnal enuresis (only in patients over the age of 5 years and if organic causes have been excluded). When initiating clomipramine for nocturnal enuresis to children and adolescents, careful consideration should be given to the benefits versus the risks for the individual. Potential alternative therapies should be considered.

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

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, phobias and panic attacks, cataplexy accompanying narcolepsy and chronic painful conditions. The use of Anafranil in children and adolescents (0-17 years of age) in these indications is therefore not recommended.

## DOSAGE AND ADMINISTRATION

Before initiating treatment with Anafranil, hypokalemia should be treated (see section 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. 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 section WARNINGS AND PRECAUTIONS and section 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.

## Depression, obsessive-compulsive syndromes, and phobias

Start treatment with -1 coated tablet of 25 mg 2-3 times daily or 1 sustained-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 4-6 tablets of 25 mg or 2 sustained-release tablets of 75 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 2-4 coated tablets of 25 mg or 1 modified-release tablet of 75 mg.

## Panic attacks, agoraphobia

Start with 10 mg daily. Depending on how the medication is tolerated, raise the dosage until the desired response is obtained. The daily dosage required varies greatly from patient to patient and lies between 25 and 100 mg. If necessary it can be increased to 150 mg. It is advisable for treatment not to be discontinued for at least 6 months and for the maintenance dose to be reduced slowly during this time.

## Cataplexy accompanying narcolepsy

Daily dose of 25-75 mg.

## Chronic painful conditions

The dosage must be individualized (10-150 mg daily), while taking account of concomitant analgesic medication (and of the possibility of reducing use of analgesics).

## Dosage and administration in special populations

### Geriatric patients (aged 65 years and older)

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.

**Nocturnal enuresis**

Initial daily dose for first one week in children aged:

5-8 years, 20-30 mg;

9-12 years, 25-50 mg;

above 12 years,25-75 mg.

The higher doses are for patients who do not respond fully to treatmentwithin one week. The coated tablets should normally be given in a single dose after the evening meal, but children who wet their beds early in the night should be given part of the dose beforehand (at 4 p.m.). Once the desired response has been achieved, treatment should be continued (for 1-3 months) and the dose gradually reduced.

No experience is available in children under 5 years.

## Renal impairment

Anafranil should be given with caution in patients with renal impairment (see section WARNINGS AND PRECAUTIONS and section CLINICAL PHARMACOLOGY).

## Hepatic impairment

Anafranil should be given with caution in patients with hepatic impairment (see section WARNINGS AND PRECAUTIONS and section CLINICAL PHARMACOLOGY).

## Method of administration

The method of administration should be adapted to the individual patient's condition. The sustained-release tablets should be swallowed whole. The Divitabs (sustained-release tablets divisible) can be halved, allowing the dosage to be adapted individually, but they should not be chewed (see section INSTRUCTIONS FOR USE AND HANDLING).

Anafranil can be administered with or without food.

## 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 INTERACTIONS). The concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated.

Recent myocardial infarction.

Congenital long QT syndrome.

## 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 pediatric, 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 behavior (suicidality) in short-term studies in children, adolescents and young adults less than 25 years old 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 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 section WARNINGS AND PRECAUTIONS subsection Treatment discontinuation).

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 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 or capsules 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 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 and elderly 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, as well as in elderly 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 DOSAGE AND ADMINISTRATION and 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 section DOSAGE AND ADMINISTRATION and section 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 section DOSAGE AND ADMINISTRATION and section 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 etiology, concomitant use of neuroleptics, withdrawal

from alcohol or drugs with anticonvulsive properties (e.g. benzodiazepines). It appears that the occurrence of seizures is dose dependent. Therefore, the recommended total daily dose of Anafranil should not be exceeded.

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 tumors of the adrenal medulla (e.g. phaeochromocytoma, 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.

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 behavioral 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 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 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 and other nervous system and psychiatric related disorders such as somnolence, disturbance in attention, confusion, disorientation, aggravation of depression, delirium etc. (see section 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 INTERACTIONS).

## 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 (≥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.

**Table 1 Tabulated summary of adverse drug reactions**

| | |
|---|---|
| **Blood and lymphatic system disorders** | |
| Very rare | Leukopenia, 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 disorder (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 | Syndrome of inappropriate antidiuretic hormone secretion (SIADH) |
| **Eye disorders** | | |
| | Very common | Accommodation disorder, vision blurred |
| | Common | Mydriasis |
| | Very rare | Glaucoma |
| **Gastrointestinal disorders** | | |
| | Very common | Nausea, dry mouth, constipation |
| | Common | Vomiting, gastrointestinal disorder, diarrhoea |
| **General disorders and administration site conditions** | | |
| | Very common | Fatigue |
| | Very rare | Oedema (local or generalised), alopecia, hyperpyrexia |
| **Hepatobiliary disorders** | | |
| | Very rare | Hepatitis with or without jaundice |
| **Immune system disorders** | | |
| | Very rare | Anaphylactic and anaphylactoid reactions including hypotension |
| **Investigations** | | |
| | Very common | Weight increased |
| | Common | Transaminases increased |
| | Very rare | Electroencephalogram abnormal |
| **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, 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 not known: Serotonin syndrome, extrapyramidal disorders (including akathisia and tardive dyskinesia).

**Musculoskeletal and connective tissue disorders**

Frequency not known: Rhabdomyolysis (as a complication of neuroleptic malignant syndrome).

**Reproductive system and breast disorders**

Frequency not known: Ejaculation failure, Ejaculation delayed.

**Investigations**

Frequency not known: Blood prolactin increased.

## 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 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 metabolize and eliminate drugs may be reduced, leading to a risk of elevated plasma concentrations at therapeutic doses.

## INTERACTIONS

### Interactions resulting in a contraindication

#### MAO inhibitors

MAO inhibitors, which are also potent CYP2D6 inhibitors *in vivo*, such as moclobemide, are contraindicated for co-administration with clomipramine.

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). 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 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 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 section DOSAGE AND ADMINISTRATION and section 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). See section DOSAGE AND ADMINISTRATION and section WARNINGS AND PRECAUTIONS. In addition

comedication with SSRIs may lead to additive effects on the serotonergic system (see serotonergic agents).

### 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 section DOSAGE AND ADMINISTRATION and section 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 co-administered with terbinafine.

**Cimetidine**

Co-administration with the histamine$_2$ ($H_2$)-receptor antagonist, cimetidine (an inhibitor of several P450 enzymes, including CYP2D6 and CYP3A4), may increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

**Oral contraceptives**

No interaction between 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 guanethidine, betanidine, reserpine, clonidine and alpha-methyldopa. Patients requiring co-medication 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 anesthetics).

### Sympathomimetic drugs

Anafranil may potentiate the cardiovascular effects of adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine (e.g. local anesthetics).

**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.

## WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

### Women of child-bearing potential

There are no data supporting any special recommendations in women of child-bearing potential.

### 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.

Neonates whose mothers had taken tricyclic antidepressants until delivery showed drug withdrawal symptoms, such as dyspnea, 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.

## 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 sustained release Anafranil. The pharmacobezoar may be radiopaque, facilitating radiologic (X-ray or CT scan) confirmation but cannot exclude the diagnosis. The formation of pharmacobezoar may cause slow but continual release and absorption of clomipramine which may lead to overdose complications, including death, hours after drug ingestion and initial treatment with gastric lavage and activated charcoal. Since gastric lavage may be ineffective and could further increase systemic drug levels, consideration should be given to physical removal of the pharmacobezoar by endoscopy or surgery in selected patients. Since these cases are 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

Somnolence, stupor, coma, ataxia, restlessness, agitation, hyperreflexia, muscle rigidity and choreoathetosis, 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.

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.

## CLINICAL PHARMACOLOGY

## Pharmacodynamic properties

### Mechanism of action

The therapeutic activity of Anafranil is believed to be based on its ability to inhibit the neuronal reuptake of noradrenaline (NA) and serotonin (5-HT) released in the synaptic cleft, with inhibition of 5-HT reuptake being the more important of these activities.

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

### Pharmacodynamic effects

Anafranil acts on the depressive syndrome as a whole, including in particular typical features such as psychomotor retardation, depressed mood, and anxiety. The clinical response usually sets in after 2-3 weeks of treatment.

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

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

## Pharmacokinetic properties

### Absorption

Following oral administration, clomipramine is completely absorbed from the gastrointestinal tract. The systemic bioavailability of unchanged clomipramine is reduced to about 50% by hepatic first-pass metabolism to the active metabolite, *N*-desmethylclomipramine.The bioavailability of clomipramine is not markedly affected by the ingestion of food. Only the onset of absorption may be slightly delayed and therefore time to peak prolonged. Coated tablets, sustained-release tablets, and capsules are bioequivalent with respect to amount absorbed.

During oral administration of constant daily doses of Anafranil, the steady-state plasma concentrations of clomipramine show a high variability between patients. The dose of 75 mg daily, administered either as coated tablets of 25 mg t.i.d. or as a sustained-release tablet of 75 mg once daily, produces steady-state plasma concentrations ranging from about 20 to 175 ng/mL.

The steady-state 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 is about 12 to 17 L/kg bodyweight. Concentrations in cerebrospinal fluid are about 2% of the plasma concentration. Clomipramine passes into maternal milk in concentrations similar to those in plasma and crosses the placenta.

### Metabolism

The primary route of clomipramine metabolism is demethylation to form the active metabolite, *N*-desmethylclomipramine. *N*-desmethylclomipramine can be formed by several P450 enzymes, primary CYP3A4, CYP2C19, and CYP1A2. Clomipramine and *N*-desmethylclomipramine are hydroxylated to form 8-hydroxyclomipramine or 8-hydroxy-*N*-desmethylclomipramine.The activity of the 8-hydroxy metabolites are not defined *in vivo*. 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 catalyzed by CYP2D6.

### Elimination

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

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

### Characteristics in patients

**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.

## CLINICAL STUDIES

No recent clinical trials have been conducted with Anafranil.

## NON-CLINICAL SAFETY DATA

According to the experimental data available, Anafranil has no mutagenic, carcinogenic or teratogenic effects. However, Anafranil has been shown to be embryotoxic in the mouse and rat at the lowest dose tested, which was 4 times the maximum recommended human dose on a body weight basis.

## INCOMPATIBILITIES

Not applicable.

## STORAGE

See folding box.

25 mg Coated tablets: protect from moisture.

10 mg Coated tablets: none.

Capsules: protect from heat and moisture.

Sustained-release tablets: Do not store above 30°C Anafranil should not be used after the date marked “EXP” on the pack.

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

## INSTRUCTIONS FOR USE AND HANDLING

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

### Manufacturer:

See folding box.

### Country Specific Package Leaflet

Information issued: January 2015.SIN

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## Novartis Pharma AG, Basel, Switzerland