SCHEDULING STATUS: S5

S5

PROPRIETARY NAMES AND DOSAGE FORMS:

ANAFRANIL 10 (tablets)

ANAFRANIL 25 (tablets)

ANAFRANIL SR 75 (divitabs)

COMPOSITION:

ANAFRANIL 10 tablets and ANAFRANIL 25 tablets contains 10 mg and 25 mg clomipramine hydrochloride respectively.

ANAFRANIL SR 75 divitabs contains 75 mg clomipramine hydrochloride in a slow release formulation.

Excipients:

ANAFRANIL 10 mg and ANAFRANIL 25 mg tablets:

Cellulose microcrystalline, copovidone (vinylpyrrolidone-vinylacetate copolymer), hypromellose (hydroxypropyl methylcellulose), iron oxide, maize starch, magnesium stearate, macrogol 8000 (polyethylene glycol 8000), povidone (polyvinylpyrrolidone), silica colloidal anhydrous, talc, titanium dioxide (E171), yellow (E172).

Each ANAFRANIL 10 mg tablet contains sugar lactose (33,250 mg) and sucrose 28,230 mg)

ANAFRANIL 25 mg tablets also contain stearic acid and glycerol (85 %).

Each ANAFRANIL 25 mg tablet contains sugar (sucrose 16,500 mg)

ANAFRANIL SR 75 divitabs:

Calcium hydrogen phosphate dihydrate, calcium stearate, hypromellose (hydroxypropyl methylcellulose), iron oxide red, macrogolglycerol hydroxystearate (polyoxyl 40 hydrogenated castor oil), polyacrylate dispersion 30 %, silica colloidal anhydrous, talc, titanium dioxide.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION:

Clomipramine has actions at several sites. These include alpha$_1$-adrenolytic, anticholinergic, antihistaminic and antiserotonergic activities.

Pharmacodynamic properties

The therapeutic activity of clomipramine is believed to be based on its ability to inhibit neuronal re-uptake of serotonin, primarily, and also noradrenaline.

Pharmacokinetic properties::

Absorption:

The active substance is completely absorbed by the oral and intramuscular routes.

Plasma concentration:

May range between 20 to 175 ng/ml after oral administration of a daily dosage of 75 mg. There are large inter-individual differences in clomipramine's distribution and clearance. Steady-state concentrations of the active metabolite desmethylclomipramine are 40 to 85 % higher than those of clomipramine. Owing to lower clearance of clomipramine, doses should be adjusted in elderly patients. The concentration in the CSF is equivalent to approximately 2 % of the plasma concentration.

Protein binding: 97,6 %.

Plasma half-life for the beta-phase of elimination: approximately 21 hours.

Distribution volume: approximately 12 litres/kg body mass.

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.

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 catalysed by CYP2D6.

Excretion:

Two-thirds in the form of water-soluble conjugates in the urine, and approximately one-third in the faeces. The quantity of unchanged clomipramine and of active metabolites excreted in the urine amounts to less than 1 % of the dose administered.

INDICATIONS:

Adults:

Treatment of depressive episodes, recurrent depressive disorders or major depression.

Cataplexy accompanying narcolepsy.

Obsessive-compulsive syndromes.

Children and adolescents:

Obsessive–compulsive syndromes in children 5 years of age and older.

CONTRAINDICATIONS:

Combination therapy with other antidepressants.

Recent myocardial infarction.

Congenital long QT syndrome.

Hypokalaemia.

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

Concomitant treatment with ANAFRANIL and MAO-inhibitors including selective, reversible MAO-inhibitors such as moclobemide is contra-indicated. In patients who have been receiving a MAO-inhibitor, ANAFRANIL should be given only after an adequate interval (14 days) has elapsed following withdrawal of the MAO-inhibitor (see INTERACTIONS) as severe interactions may occur (e.g. hyperactivity, hypertensive crisis, hyperpyrexia, spasticity, convulsions, coma). The same caution should be observed when administering a MAO-inhibitor after treatment with ANAFRANIL.

WARNINGS AND SPECIAL PRECAUTIONS

This medicine should at all times be kept out of the reach of children, as relatively small overdoses may be fatal to them.

Caution should be exercised when prescribing ANAFRANIL in patients with:

- Cardiovascular insufficiency, atrioventricular block (grades I to III) and dysrhythmias.
- Narrow-angle glaucoma.
- Disorders of micturition due to an impeded flow of urine (e.g. in diseases of the prostate).
- A low convulsion threshold (e.g. due to brain damage of varying aetiology, epilepsy, alcoholism).
- Severe hepatic or renal diseases.
- Tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), in whom the medicine may provoke hypertensive crises.
- Simultaneous treatment with other tricyclic antidepressants and electroconvulsive therapy should only be resorted to under careful supervision.

Anaphylactic shock:

Isolated cases of anaphylactic shock have been reported.

Risk of suicide:

Risk of suicide is inherent to severe depression and may persist until significant remission occurs. Patients with depressive disorders, both adult and paediatric, may experience worsening of depression and/or suicidality or other psychiatric symptoms, whether or not they are taking antidepressant medication.

Antidepressants increased the risk of suicidal thinking and behaviour (suicidality) in short-term studies in children and adolescents 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 SIDE 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.

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

Prescriptions for ANAFRANIL should be written for the smallest quantity of tablets or divitabs consistent with good patient management, in order to reduce the risk of overdose.

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 and cataplexy accompanying narcolepsy. The use of ANAFRANIL in children and adolescents (0-17 years of age) in these indications is therefore not recommended.

Other psychiatric effects:
Activation of psychosis has occasionally been observed in patients with schizophrenia receiving ANAFRANIL.

Caution should be observed with patients suffering from a bipolar disorder, as hypomania or mania can be precipitated in such patients. Withdraw ANAFRANIL immediately if the depression turns into a manic phase.

In predisposed and elderly patients, ANAFRANIL may, particularly at night, provoke pharmacogenic (delirious) psychoses, which may disappear without treatment within a few days of withdrawing the medicine.

Cardiac and vascular disorders:

Tricyclic antidepressants should be employed with caution in patients with cardiovascular disorders, especially those who have a history of conduction disorders and elderly patients. Monitoring of cardiovascular function and ECG is advised in such cases.

There is 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 medicines that can cause accumulation of clomipramine should be avoided. Equally, concomitant administration of medicines that can prolong the QTc interval should be avoided (see *Dosage and Directions for Use* and *Interactions*). 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 DOSAGE AND DIRECTIONS FOR USE AND INTERACTIONS).

Before initiating treatment it is advisable to check the patient's blood pressure because hypotensives and individuals with a labile circulation may react to the medicine with a fall in blood pressure. This can be controlled by reducing the dosage.

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 ANAFRANIL is administered with serotonergic co-medications such as SSRIs, SNaRIs, tricyclic antidepressants or lithium (see DOSAGE AND DIRECTIONS FOR USE AND INTERACTIONS). For fluoxetine a washout period of two to three weeks is advised before and after treatment with fluoxetine.

Convulsions:

ANAFRANIL should be used with caution in patients with epilepsy or in patients prone to convulsions or seizures; and also in other predisposing factors such as brain damage, concomitant use of neuroleptics, withdrawal from alcohol or medicines with anticonvulsive properties (e.g. benzodiazepines). The occurrence of seizures is dose related; therefore the recommended total daily dose of ANAFRANIL should not be exceeded.

Anticholinergic effects:

Narrow-angle glaucoma may be aggravated.

Particular caution is indicated when employing ANAFRANIL in the presence of disorders of micturition due to an impeded flow of urine (e.g. in diseases of the prostate), since in patients suffering from prostatism, urinary retention may be precipitated.

Decreased lacrimation and accumulation of mucoid secretion due to the anticholinergic properties of tricyclic antidepressants may cause damage to the corneal epithelium in patients with contact lenses. The use of artificial tears is recommended in these patients.

The simultaneous administration of anticholinergic agents may be dangerous (see INTERACTIONS*)*.

Specific treatment populations:

Caution is indicated in patients with hyperthyroidism or in the case of concomitant treatment with thyroid preparations, since aggravation of unwanted cardiac effects may occur owing to the anticholinergic action.

In patients with liver disease, periodic monitoring of hepatic enzyme levels is recommended.

ANAFRANIL may cause paralytic ileus especially in the elderly and in bedridden patients and those patients suffering from chronic constipation.

Prolonged treatment with ANAFRANIL can lead to an increased incidence of dental caries. Regular dental check-ups are therefore advisable during long-term treatment.

Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

White blood cell count:

Occurrences of agranulocytosis have been connected with the use of ANAFRANIL. It is therefore also advisable to perform blood counts during treatment with ANAFRANIL, especially if the patient develops fever, an influenzal infection or sore throat.

Anaesthesia:

Before general or local anaesthesia, the anaesthetist should be told that the patient has been receiving ANAFRANIL.

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 *Side-Effects*, for a description of the risks of discontinuation of ANAFRANIL).

The risks of central nervous system depression are greater when administered together with other central nervous system depressants (e.g. alcohol and barbiturates) and should therefore not usually be administered simultaneously. Since ANAFRANIL may diminish alcohol tolerance, patients should be advised to abstain from alcohol while under treatment.

Owing to its antagonistic effect on dopamine, ANAFRANIL may increase prolactin secretion. Blood sugar concentrations may be altered in diabetic patients.

Lactose and sucrose

ANAFRANIL 10 contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ANAFRANIL 10.

ANAFRANIL 10 and ANAFRANIL 25 contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take ANAFRANIL 10 and ANAFRANIL 25.

ANAFRANIL 10 contains lactose and sucrose and ANAFRANIL 25 contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Effects on ability to drive and use machines:

At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb heights or operate machinery for at least several days. In these situations impaired decision-making could lead to accidents and caution is always necessary while on ANAFRANIL therapy.

INTERACTIONS:

Pharmacodynamic interactions:

Adrenergic neurone blockers:

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).

Anticholinergic agents:

ANAFRANIL may potentiate the effects of anticholinergic agents (e.g. phenothiazine, antiparkinsonian agents, antihistamines, atropine, biperiden).

CNS depressants:

The risks of central nervous system depression are greater when ANAFRANIL is administered together with other central nervous system depressants (e.g. alcohol and barbiturates) and should therefore not usually be administered simultaneously.

Diuretics:

Co-medication of ANAFRANIL with 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 DOSAGE AND DIRECTIONS FOR USE AND WARNINGS AND SPECIAL PRECAUTIONS).

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). 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 *Contra-Indications* section).

Selective serotonin re-uptake inhibitors (SSRI):

Concomitant administration of ANAFRANIL with selective serotonin re-uptake inhibitors (e.g. fluoxetine and fluvoxamine) 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 DOSAGE AND DIRECTIONS FOR USE AND WARNINGS AND SPECIAL PRECAUTIONS). For fluoxetine, a washout period of two to three weeks is advised before and after treatment with fluoxetine.

Sympathomimetic medicines:

ANAFRANIL may potentiate the cardiovascular effects of noradrenaline or adrenaline and the use of local anaesthetics and nose drops containing these vasoconstrictors should be avoided as hypertensive reactions may occur.

Pharmacokinetic interactions:

ANAFRANIL (clomipramine) is predominantly 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 medicine. Several cytochrome P450s are involved in the demethylation, mainly CYP3A4, CYP2C19 and CYP1A2. Elimination of both active components is by hydroxylation and this is catalyzed by CYP2D6.

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 metaboliser phenotype, converting them to a poor-metaboliser 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.

- MAO inhibitors, which are also potent CYP2D6 inhibitors *in vivo*, such as moclobemide, are contraindicated for co-administration with clomipramine (see CONTRAINDICATIONS).
- Antidysrhythmic medicines (such as quinidine and propafenone), which are potent inhibitors of CYP2D6, should not be used in combination with tricyclic antidepressants.
- 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 DOSAGE AND DIRECTIONS FOR USE AND WARNINGS AND SPECIAL PRECAUTIONS).
- Co-medication of neuroleptics (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.
- Co-administration with 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.

- No interaction between chronic oral contraceptive use (15 or 30 micrograms ethinyl oestradiol daily) and ANAFRANIL (25 mg daily) has been documented. Oestrogens 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 oestrogen (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 oestrogen regimens. Monitoring therapeutic response of tricyclic antidepressants at high dose oestrogen 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, and a dose reduction of the tricyclic antidepressant may be necessary.
- Some tricyclic antidepressants may potentiate the anticoagulant effect of coumarin medicines, 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 medicines.

Concomitant administration of medicines known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19, and/or CYP1A2 may accelerate the metabolism and decrease the efficacy of ANAFRANIL.

- 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 medicines. In cigarette smokers, clomipramine steady-state plasma concentrations were decreased 2-fold compared to non-smokers (no change in *N*-desmethylclomipramine).

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 metabolisers.

PREGNANCY AND LACTATION:

Pregnancy

Safety in pregnancy has not been established. There have been reports of withdrawal symptoms in babies born to mothers who received ANAFRANIL shortly before delivery.

Lactation

Since the active substance passes into the breast milk, nursing mothers receiving ANAFRANIL should not breast-feed their infants.

DOSAGE AND DIRECTIONS FOR USE:

Medical supervision is essential.

Before initiating treatment with ANAFRANIL, hypokalaemia should be treated (see WARNINGS AND SPECIAL PRECAUTIONS).

The dosage and mode of administration should be determined individually and adapted to the patient's condition.

The divitabs can be halved, but must not be chewed. They are fractionable into two equal halves allowing flexible dosages.

The lowest dose possible, in order to achieve an optimal therapeutic effect should be used and the dosage should be built up gradually to ensure maximum tolerability. Caution should be exercised in elderly and adolescent patients.

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 medicines that prolong QTc interval or other serotonergic agents are co-administered (see WARNINGS AND SPECIAL PRECAUTIONS AND INTERACTIONS).

Adults

Depression and obsessive-compulsive disorders:

- Oral: Treatment should be initiated with 1 tablet of 25 mg 2 to 3 times daily or 1 ANAFRANIL SR 75 divitab of 75 mg once a day (preferably in the evening). The daily dosage should be raised stepwise, e.g.

25 mg every few days, (depending on how the medication is tolerated) to 2 to 4 tablets of 25 mg or 1 ANAFRANIL SR 75 divitab during the first week of treatment. Higher doses may be needed in some patients, particularly those suffering from obsessional disorders. A maximum dose of 250 mg should not be exceeded.

Once a distinct improvement has occurred, adjust the daily dosage to a maintenance level averaging two to four 25 mg tablets or one SR 75 divitab.

ANAFRANIL may be given traditionally in divided doses throughout the day or may be administered in a single dose at bedtime by administration of the doses of 10 mg or 25 mg tablets or sustained release divitabs of 75 mg. The dosage should be built up gradually for the single bedtime dose, in order to ensure maximum tolerability.

Cataplexy accompanying narcolepsy:

ANAFRANIL should be given orally in a daily dose of 25 to 75 mg.

Geriatrics:

Initiate treatment with 1 tablet of 10 mg daily. Gradually raise the dosage to an optimum level of 30 to 50 mg daily, which should be reached after about 10 days and then adhered to until the end of treatment.

Children and adolescents:

Obsessive-compulsive syndromes*:*

The starting dose is 25 mg daily and should be gradually increased (also given in divided doses) during the first two 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.

SIDE EFFECTS

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, transient fatigue, restlessness, increased appetite.

Common: Confusion, disorientation, hallucinations (particularly in geriatric patients and patients suffering from Parkinson's disease), anxiety states, agitation, sleep disturbances, mania, hypomania, aggressiveness, impaired memory, depersonalisation, depression aggravated, impaired concentration, insomnia, nightmares, yawning.

Uncommon: Activation of psychotic symptoms.

The use of ANAFRANIL does not preclude the possibility of additional treatment with neuroleptic agents, hypnotics or minor tranquillisers.

Neurological effects:

Very common: Dizziness, tremor, headache, myoclonus.

Common: Delirium, speech disorders, paraesthesia, muscle weakness, muscle hypertonia.

Uncommon: Convulsions, ataxia,

Very rare: EEG changes, hyperpyrexia, neuroleptic malignant syndrome, peripheral neuropathy.

Extrapyramidal side-effects such as speech difficulties and gastric irritation with nausea and vomiting can occur.

Anticholinergic effects:

Very common: Dry mouth, sweating, constipation, disorders of visual accommodation and blurred vision, disturbances of micturition.

Common: Hot flushes, mydriasis.

Very rare: Glaucoma, urinary retention.

When anticholinergic effects are severe the medicine should be discontinued or reduced.

Cardiovascular system:

Common: Sinus tachycardia, palpitations, postural hypotension, clinically insignificant ECG changes (e.g. ST and T changes), in patients of normal cardiac status.

Uncommon: Dysrhythmias, increased blood pressure,

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).

In patients suffering from cardiac disease, special caution should be observed. Regular cardiological and electrocardiographic examination is advised.

Gastrointestinal tract:

Very common: Nausea

Common: Vomiting, abdominal disorders, diarrhoea, anorexia.

Liver:

Common: Elevated transaminases.

Very rare: Hepatitis with or without jaundice, stomatitis.

Skin:

Common: Allergic skin reactions (skin rash, urticaria), photosensitivity, pruritus.

Very rare: Oedema (local or generalised), hair loss. Local reactions after intravenous injections (thrombophlebitis, lymphangitis, burning sensation and allergic skin reactions).

Withdraw the medicine if allergic skin reactions appear.

Endocrine system and metabolism:

Very common: Weight gain, disturbances of libido and potency

Common: Galactorrhoea, breast enlargement.

Very rare: SIADH (inappropriate antidiuretic hormone secretion syndrome).

Hypersensitivity:

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

Blood:

Very rare: Leucopenia, agranulocytosis, thrombocytopenia, eosinophilia and purpura.

Sense organs:

Common: Taste disturbances, tinnitus.

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 WARNINGS AND SPECIAL PRECAUTIONS).

Note: Elderly patients are more prone to all these effects, and therapy should be initiated at lower than standard doses in the elderly.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Signs and symptoms

Overdosage and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects (which set in about a half to two hours after ingestion) and cardiotoxicity. The following symptoms and signs are characteristic of acute overdosage:

Central nervous system:

Drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity and choreoathetoid movements, convulsions. In addition, symptoms consistent with Serotonin Syndrome (e.g. hyperpyrexia, myoclonus, delirium and coma) may be observed.

Cardiovascular system:

Hypotension, tachycardia, arrhythmias, QTc prolongation and dysrhythmias 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.

Since physostigmine increases the risk of seizures occurring, it should not be used.

Attempts should be made to eliminate the medicine by inducing vomiting if the patient is alert and/or irrigating the stomach. If the patient is not alert, secure the airway with a cuffed endotracheal tube before beginning lavage, and do not induce vomiting. This is recommended for up to 12 hours or even longer after overdose.

The patient should be transferred to hospital and vital functions safeguarded.

Activated charcoal should be administered.

Treatment is symptomatic and supportive.

Vital functions (including the ECG) should be monitored for not less than 5 days.

IDENTIFICATION:

ANAFRANIL 10 mg tablets: light yellow, triangular, biconvex, sugar-coated tablets. Apex to base of triangle approximately 5,8 mm. Thickness approximately 3,3 mm.

ANAFRANIL 25 mg tablets: light yellow, sugar-coated, round, biconvex tablets. Diameter approximately 5,6 mm. Thickness approximately 3,5 mm.

ANAFRANIL SR 75 divitabs: rose coloured, film-coated, capsule-shaped, biconvex, divisible tablets, scored on the one side. Length approximately 13,2 mm. Width approximately 5,2 mm. Thickness approximately 4,6 mm.

PRESENTATION:

ANAFRANIL is supplied as 10 mg and 25 mg tablets in blister packs of 50, as SR 75 divitabs in blister packs of 30.

STORAGE INSTRUCTIONS:

For tablets: Store at or below 30 °C and protect from moisture and light.

For divitabs: Store at or below 30 °C and protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ANAFRANIL 10 mg	C/1.2/182
ANAFRANIL 25 mg	B1532 (Act 101 of 1965)
ANAFRANIL SR 75	W/1.2/140

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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