Prescribing Information

1. Name of the medicinal product

Anafranil 25 mg

Anafranil SR 75 mg tablets

2. Composition

Active substance: Clomipramine hydrochloride

For the full list of excipients, see section 6.1.

3. Pharmaceutical form and quantity of active substance per unit

Anafranil 25 mg: Coated tablets containing 25 mg clomipramine hydrochloride

Anafranil SR 75 mg tablets: Slow-release divisible tablets (“Divitabs”) containing 75 mg clomipramine hydrochloride

4.

4.1. Therapeutic indications

Depression of varying origin

In children and adolescents, there is not sufficient evidence of safety and efficacy of Anafranil in the treatment of depressive states of varying aetiology and symptomatology. The use of Anafranil in children and adolescents (0-17 years of age) in this indication is therefore not recommended.

Obsessive-compulsive syndromes

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

4.2. Dosage and administration

Before initiating treatment with Anafranil, hypokalemia should be treated (see section 4.4 Warnings and precautions).

The dosage should be adapted to the individual patient's condition. The aim is to achieve an optimum effect while keeping the doses as low as possible and increasing them cautiously.

After a response has been obtained, maintenance therapy should be continued at the optimum dose to avoid relapse. Patients with a history of recurrent depression require maintenance treatment for a longer duration. Duration of maintenance treatment and need for further treatment should be reviewed periodically.

As a precaution against possible QTc prolongation and serotonergic toxicity, adherence to the recommended doses of Anafranil is advised and any increase in dose should be made with caution if drugs that prolong QT interval or other serotonergic agents are co-administered (see sections 4.4 Warnings and precautions and 4.5 Interactions).

Abrupt discontinuation of Anafranil therapy should be avoided because of possible withdrawal symptoms. Therefore, dosage should be stopped gradually after regular use for long duration and the patient should be monitored carefully when Anafranil therapy is discontinued.

Immediate release formulations (coated tablets) and slow-release tablets can be used inter-changeably in equivalent doses.

Depression and obsessive-compulsive syndromes

Start treatment with 50-75 mg/day (1 coated tablet of 25 mg 2-3 times daily or 1 slow-release tablet of 75 mg once daily [preferably in the evening]). Raise the daily dosage stepwise, e.g. 25 mg every few days, (depending on how the medication is tolerated) to 100-150 mg, during the first week of treatment. In severe cases, this dosage can be increased up to a maximum of 250 mg daily. Once there is a distinct improvement, adjust the daily dosage to a maintenance level of about 50-100 mg.

Dosage and administration in special populations

Geriatric population

Elderly patients generally show a stronger response to Anafranil than patients of intermediate age groups, Anafranil should be used with caution in elderly patients and doses should be increased cautiously. Start treatment with 10 mg daily. Gradually raise the dosage to an optimum level of 30-50 mg daily, which should be reached after about 10 days and then maintained until the end of treatment.

Children and Adolescents

Adolescents generally show a stronger response to Anafranil than patients of intermediate age groups, Anafranil should be used with caution in adolescents and doses should be increased cautiously.

Obsessive-compulsive syndromes

The starting dose is 25 mg daily and should be gradually increased (also given in divided doses) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller.

No experience is available in children under 5 years.

Renal impairment

Anafranil should be given with caution in patients with renal impairment (see section 4.4 Warnings and precautions).

Hepatic impairment

Anafranil should be given with caution in patients with hepatic impairment (see section 4.4 Warnings and precautions).

Method of administration

The method of administration should be adapted to the individual patient's condition. The Divitabs (slow-release tablets divisible) can be halved, allowing the dosage to be adapted individually, but they should not be chewed.

Anafranil can be administered with or without food.

4.3. Contraindications

Hypersensitivity to clomipramine or any of the excipients of Anafranil or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group.

Antiarrhythmics such as quinidine and propafenone, which are potent CYP2D6 inhibitors, must not be combined with tricyclic antidepressants.

Anafranil must not be given in combination with – or within 14 days before or after – treatment with a non-selective, irreversible or a selective, irreversible MAO inhibitor (see 4.5 Interactions). Concomitant treatment with a selective, reversible MAO-A inhibitor such as moclobemide or a non-selective, reversible MAO inhibitor such as linezolid is also contraindicated (see 4.5 Interactions).

Use is also contraindicated in patients with recent myocardial infarction or congenital long QTc syndrome.

Anafranil should not be administered in patients with

- acute intoxication with CNS depressants such as hypnotics, analgesics or psychotropic agents or with alcohol
- acute urinary retention
- acute delirium
- untreated narrow-angle glaucoma
- prostatic hypertrophy with residual urine retention
- pyloric stenosis
- paralytic ileus.

4.4. Warnings and precautions

Caution is required when switching treatment to another dosage form and/or another medicinal product with the same active substance. The patient should be monitored appropriately.

Risk of suicide

Depression is associated with an elevated risk of suicidal ideation, self-harm and completed suicide. Suicidal ideation and suicidal behaviour may also be exacerbated during antidepressant treatment.

Anafranil should not be used to treat depression in children and adolescents aged under 18 years. In studies on treatment of depression in this age group tricyclic antidepressants showed no therapeutic benefit.

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, adolescents and young adults (up to 25 years of age). A similar effect cannot be ruled out for other antidepressants (including Anafranil), for which such data is 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), particularly at the start of treatment and when the dose is changed. Patients must also be closely monitored after treatment ends because such symptoms may occur as signs of withdrawal or incipient relapse.

Psychiatric diagnoses other than depression 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 carers of patients should be advised to be vigilant for the emergence of other psychiatric symptoms (see 4.8 Adverse effects) and suicidality and to report them immediately to the attending physician.

Antidepressant therapy is not a suitable means of avoiding the hospitalisation required in cases of self-endangerment. The medicinal product should be prescribed in the smallest suitable pack size, particularly at the start of treatment, 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. Anafranil should be prescribed at the lowest possible dose consistent with optimum patient management to reduce the risk of overdose.

Other psychiatric effects

Activation of psychosis has occasionally been observed in schizophrenic patients receiving tricyclic antidepressants. As a result of their activating effect, tricyclic antidepressants may cause increased anxiety, inner restlessness and agitation in patients with agitation or concomitant schizophrenic symptoms.

Hypomanic and manic episodes have been reported during depressive phases in patients with bipolar affective disorders treated with tricyclic antidepressants. In such cases it may be necessary to reduce the dose of, or stop, Anafranil and administer an antimanic 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. This resolves without treatment within a few days of stopping the medicinal product.

Convulsions

Tricyclic antidepressants lower the convulsion threshold. Anafranil must therefore be used with extreme caution in patients with epilepsy or other predisposing factors, e.g. brain damage of varying aetiology, co-administration of neuroleptics, withdrawal of alcohol or of medicinal products with anticonvulsant properties (e.g. benzodiazepines). The occurrence of seizures is apparently dose-dependent. The recommended total daily dose must therefore not be exceeded.

Patients should be kept under close supervision when tricyclic antidepressants are given concomitantly with electroconvulsive therapy.

Anticholinergic effects

Due to its anticholinergic properties Anafranil must be used with caution in patients with a history of increased intraocular pressure, narrow-angle glaucoma or urinary retention (e.g. due to prostate disease).

Decreased lacrimation and accumulation of mucoid secretions caused by the anticholinergic properties of tricyclic antidepressants may damage the corneal epithelium in contact lens wearers.

Serotonin syndrome

Due to the risk of serotonergic toxic reactions, it is advisable to adhere to the recommended dose. Serotonin syndrome with symptoms such as hyperpyrexia, myoclonus, restlessness, epileptic seizures, delirium and coma may occur when clomipramine is co-administered with serotonergic medicinal products such as SSRIs, SNRIs, tricyclic antidepressants, lithium, triptans, L-tryptophan, tramadol, fentanyl, Hypericum or sibutramine (see 4.2 Dosage/Administration and 4.5 Interactions). With regard to fluoxetine a washout period of two to three weeks is advised before and after treatment with this substance.

Cardiovascular disorders

Anafranil should be administered with particular caution in patients with cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders (e.g., grade I-III AV block) or arrhythmias. Monitoring of cardiac function and ECGs is indicated in such cases and in elderly patients.

There may be a risk of QTc prolongation and atypical ventricular tachycardia when doses or plasma concentrations of clomipramine are elevated, as occurs during co-medication with selective serotonin reuptake inhibitors (SSRIs) or serotonin-noradrenaline reuptake inhibitors (SNRIs) (see 4.5 Interactions). Therefore, co-administration of medicinal products that can cause accumulation of clomipramine must be avoided. Medicinal products that can prolong the QTc interval should also not be co-administered.

It is established that hypokalaemia is a risk factor for QTc prolongation and torsades de pointes. Hypokalaemia should therefore be treated before initiating Anafranil therapy and caution is required when using Anafranil in combination with SSRIs, SNRIs or diuretics (see 4.5 Interactions).

A blood pressure test is indicated before starting treatment as patients with hypotension or circulatory instability may react with a drop in blood pressure.

Special populations and long-term therapy

Caution is required in patients with chronic constipation. Paralytic ileus may occur during tricyclic antidepressant treatment, particularly in elderly and bed-ridden patients.

In patients with liver or kidney disease it is recommended to regularly monitor liver enzymes and kidney function and, if required, plasma levels of the active substance and its metabolites.

Caution is required when giving tricyclic antidepressants to patients with severe liver disease and tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma) as they may provoke hypertensive crises in these patients.

Caution is required in patients with hyperthyroidism or patients receiving thyroid preparations since the anticholinergic action of the medicinal product is generally expected to exacerbate adverse cardiac effects.

Increases in dental caries and oral mucosal changes have been reported during long-term treatment with tricyclic antidepressants. Regular dental check-ups are therefore recommended during long-term treatment.

No data are available on the safety of long-term use in children and adolescents regarding growth, maturation and cognitive and behavioural development.

Hypersensitivity reactions

Isolated cases of anaphylactic shock have been observed.

White blood cell count

Although there have only been isolated reports of changes in white blood cell count during treatment with Anafranil, blood counts should be regularly checked and monitoring for symptoms such as fever and angina carried out, particularly during the first few months of treatment and during long-term treatment. Anafranil must be discontinued in the event of a pathological decrease in neutrophil count.

Anaesthesia

Before general or local anaesthesia, the anaesthetist must be informed of Anafranil treatment.

Other

Hyperthermia (a symptom of neuroleptic malignant syndrome) has been reported during concomitant treatment with Anafranil and neuroleptics.

Discontinuation of treatment

Abrupt discontinuation of the medicinal product is to be avoided as adverse effects may occur. If treatment has to be discontinued, the dose should be tapered as rapidly as possible. It should always be borne in mind that abrupt discontinuation may be associated with certain symptoms (see 4.8 Adverse effects).

Lactose and sucrose

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.

4.5. Interactions

Pharmacodynamic interactions

Monoamine oxidase (MAO) inhibitors

Anafranil must not be given for at least 2 weeks following discontinuation of treatment with a non-selective, irreversible or a selective, irreversible MAO inhibitor as severe symptoms may otherwise occur, e.g. hypertensive crisis, hyperpyrexia, as well as symptoms associated with serotonin syndrome such as myoclonus, agitation, convulsions, delirium and coma. The same applies when giving an MAO inhibitor following treatment with Anafranil. In any case Anafranil

or the MAO inhibitor should be initiated thereafter in small, gradually increasing doses and the effects monitored (see 4.3 Contraindications).

There is evidence to suggest that Anafranil may be given as early as 24 h 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 following treatment with Anafranil.

The antibiotic linezolid is a non-selective, reversible MAO inhibitor and should therefore not be used in patients being treated with clomipramine.

Selective serotonin reuptake inhibitors (SSRIs)

Co-administration may result in an additive effect on the serotonergic system.

Serotonergic agents

Serotonin syndrome may occur when clomipramine is co-administered with serotonergic medicinal products such as selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants or lithium (see 4.2 Dosage/Administration and 4.4 Warnings and precautions). With regard to fluoxetine a washout period of two to three weeks is advised before and after treatment with this substance.

Adrenergic neurone blockers:

Anafranil may diminish or negate the antihypertensive effect of guanethidine, betanidine, reserpine, clonidine and alpha-methyldopa. In patients requiring treatment for hypertension, antihypertensives with a different mechanism of action (e.g. vasodilators or beta blockers) should therefore be used.

Sympathomimetics

The cardiovascular effect of adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine (e.g. in local anaesthetics) may be potentiated by Anafranil.

CNS depressants

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

Anticholinergics

Tricyclic antidepressants may potentiate the effect of these medicinal products (e.g. phenothiazine, antiparkinsonian agents, antihistamines, atropine and biperiden) on the eyes, central nervous system, intestine and bladder. There is a risk of hyperthermia.

Diuretics

Co-medication 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.

It might be necessary to correct other possible electrolyte disorders, in particular hypomagnesaemia, prior to initiating treatment with Anafranil.

Pharmacokinetic interactions

Anafranil (clomipramine) is predominately eliminated in metabolised form. The primary route of metabolism is demethylation to the active metabolite, N-desmethylclomipramine, followed by hydroxylation and further conjugation of N-desmethylclomipramine and the parent drug. Several

cytochrome P450s are involved in the demethylation, mainly CYP3A4, CYP2C19 and CYP1A2. Both active substances are eliminated by hydroxylation catalysed by CYP2D6.

Co-administration of CYP2D6 inhibitors may lead to an increase in the concentration of both active substances, up to approximately 3-fold in patients with a debrisoquine/sparteine extensive metaboliser phenotype, converting them to the poor-metaboliser phenotype. Co-administration of inhibitors of CYP1A2, CYP2C19 and CYP3A4 can be expected to increase concentrations of clomipramine and decrease concentrations of N-desmethylclomipramine, thus not necessarily affecting the overall pharmacology.

- MAO inhibitors such as moclobemide, which are also potent CYP2D6 inhibitors *in vivo*, must not be co-administered with clomipramine (see 4.3 Contraindications).
- Antiarrhythmics such as quinidine and propafenone, which are potent CYP2D6 inhibitors, must not be combined with tricyclic antidepressants.
- SSRIs such as fluoxetine, paroxetine, or sertraline, which inhibit CYP2D6, and SSRIs such as fluvoxamine, which inhibit other CYP enzymes – including CYP1A2 and CYP2C19 – may also increase clomipramine plasma levels, with corresponding adverse effects. Steady-state serum levels of clomipramine increased approximately 4-fold following co-administration of fluvoxamine, while N-desmethylclomipramine levels were approximately halved (see 4.2 Dosage/Administration and 4.4 Warnings and precautions).
- Concomitant treatment with neuroleptics, e.g. phenothiazines, may result in increased plasma levels of tricyclic antidepressants, a lowered epileptic seizure threshold and seizures. Combination with thioridazine may cause severe arrhythmias.
- Oral terbinafine, a potent CYP2D6 inhibitor, may lead to increased exposure and accumulation of clomipramine and its N-demethylated metabolite. A suitable dose adjustment may therefore be necessary when Anafranil is co-administered with terbinafine.
- Combination with the histamine H2-receptor antagonist cimetidine (an inhibitor of several P450 enzymes, including CYP2D6 and CYP3A4) may increase plasma levels of tricyclic antidepressants, whose dose should therefore be reduced.
- No interaction has been demonstrated between 25 mg Anafranil daily and long-term use of oral ovulation inhibitors (15 or 30 µg ethinyl oestradiol daily). Oestrogens are not known to be inhibitors of CYP2D6, the major enzyme involved in clomipramine clearance; therefore, no interaction is expected. Increases in imipramine bioavailability, therapeutic effect and adverse effects have been observed in patients given high doses of oestrogen (50 µg daily) concomitantly with the tricyclic antidepressant imipramine. However, the relevance of these observations for clomipramine and lower-dosed oestrogen is unclear. It is recommended to monitor the therapeutic response to tricyclic antidepressants when high doses of oestrogen (50 µg daily) are given and, if necessary, adjust the dosage.
- Methylphenidate may also increase concentrations of tricyclic antidepressants by inhibiting their metabolism; a dose reduction of the tricyclic antidepressant may become necessary.

- Co-administration of valproate with clomipramine may inhibit the CYP2C metabolism and/or the UGT enzyme and thereby increase serum levels of clomipramine and desmethylclomipramine.
- Co-administration of Anafranil and grapefruit, grapefruit juice or cranberry juice may modify the plasma concentration of clomipramine.
- Some tricyclic antidepressants may potentiate the anticoagulant effect of coumarins 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 suggested for this medicinal product class. Co-administration of substances that induce cytochrome P450 enzymes (in particular CYP3A4, CYP2C19 and/or CYP1A2) may accelerate clomipramine metabolism and reduce the efficacy of Anafranil.
- CYP3A4 and CYP2C19 inducers such as rifampicin or anticonvulsants (e.g. barbiturates, carbamazepine, phenobarbital and phenytoin) may lower plasma concentrations of clomipramine.
- Inducers of CYP1A2 (e.g. nicotine/components of cigarette smoke) lower plasma concentrations of tricyclic antidepressants. Steady-state plasma concentrations in cigarette smokers were half those of non-smokers (no change in plasma concentrations of N-desmethyl-clomipramine). Clomipramine is also an *in vitro* (Ki = 2.2 µM) and *in vivo* inhibitor of CYP2D6 activity (sparteine oxidation) and may therefore cause increased concentrations of co-administered substances that are primarily cleared by CYP2D6 in extensive metabolisers.
- Co-administration of ion-exchange resins such as cholestyramine or colestipol may reduce plasma levels of clomipramine. It is recommended to stagger the doses of clomipramine and resin so that clomipramine is administered either 2 hours before or 4-6 hours after the ion-exchange resin.
- Co-administration of Anafranil and St. John's wort (*Hypericum perforatum*) may reduce plasma concentrations of clomipramine.

4.6. Pregnancy/Breast-feeding

Anafranil should not be used in women of child-bearing potential who do not use contraception.

There is clear evidence of risks to the human fetus, but this may be outweighed by the therapeutic benefit to the mother. As there have been isolated reports of a possible connection between tricyclic antidepressants and adverse effects on the fetus (developmental disorders), use of Anafranil must be avoided during pregnancy and must only be considered if absolutely essential and if there is no low-risk alternative.

Neonates whose mothers had taken tricyclic antidepressants up to birth showed symptoms such as respiratory disorders, lethargy, colic, increased irritability, hypotension or hypertension, trembling, convulsions and epileptic seizures during the first few hours or days.

To avoid such symptoms, Anafranil should be stopped at least 7 weeks before the estimated date of delivery, if medically justified.

Breast-feeding

As the active substance is excreted in breast milk, either breast-feeding should be discontinued or the medicinal product should be gradually withdrawn.

4.7. Effects on ability to drive and use machines

Patients should be informed that blurred vision, somnolence and other CNS symptoms (see 4.8 Adverse effects) may occur during Anafranil treatment, in which case they should not drive, use machines or perform any other activities requiring complete alertness. Patients should also be informed that these effects may be potentiated by alcohol or other medicinal products (see 4.5 Interactions).

4.8. Adverse effects

Most adverse effects are usually transient, disappearing as treatment continues or following dose reduction. They do not always correlate with plasma concentrations or dose. It is often difficult to distinguish certain adverse effects from symptoms of depression, e.g. fatigue, sleep disorders, agitation, anxiety, constipation and dry mouth.

If severe neurological or mental adverse effects occur, Anafranil must be withdrawn.

Elderly patients (aged 65 years and over)

No data are available from clinical studies. The following generally applies: Elderly patients are particularly susceptible to anticholinergic, neurological, mental and cardiovascular effects. Their ability to metabolise and eliminate medicinal products is altered by age, leading to a risk of elevated plasma concentrations even at therapeutic doses.

Frequencies

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

Blood and lymphatic system disorders

Very rare: Leukopenia, 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, micturition disorders.

Common: Hot flushes, mydriasis.

Very rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorders

Very common: Weight increase.

Psychiatric disorders

Very common: Somnolence, transient fatigue, inner restlessness, increased appetite.

Common: Confusion accompanied by disorientation and hallucinations (particularly in geriatric patients and patients with Parkinson's disease), anxiety, agitation, sleep disorders, mania, hypomania, aggressiveness, memory disorders, yawning, behavioural changes, insomnia, nightmares, increased depression, concentration disorders.

Uncommon: Activation of psychotic symptoms.

Nervous system disorders

Very common: Dizziness, tremor, headache, myoclonus.

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

Uncommon: Seizures, ataxia.

Very rare: EEG changes, hyperpyrexia, extrapyramidal symptoms (including tardive dyskinesia), drug fever, neuroleptic malignant syndrome.

Eye disorders

Very common: Accommodation disorders, blurred vision.

Very rare: Glaucoma.

Ear and labyrinth disorders

Common: Tinnitus.

Cardiac disorders

Common: Sinus tachycardia, palpitations, clinically irrelevant ECG changes (e.g. T and ST changes) in patients with normal cardiac status.

Uncommon: Arrhythmias, increased blood pressure.

Very rare: Conduction disorders (e.g. widening of QRS complex, QT interval prolongation, PQ changes, bundle branch block), torsade de pointes in patients with hypokalaemia.

Vascular disorders

Common: Orthostatic hypotension.

Gastrointestinal disorders

Very common: Constipation.

Common: Nausea.

Uncommon: Vomiting, abdominal disorders, diarrhoea, anorexia, dysgeusia.

Hepatobiliary disorders

Common: Increased transaminases.

Very rare: Hepatitis with or without jaundice.

Skin and subcutaneous tissue disorders

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

Very rare: Hair loss.

Renal and urinary disorders

Very rare: Water retention.

Reproductive system and breast disorders

Common: Libido disorders and potency disturbances.

Uncommon: Galactorrhoea, breast enlargement.

General disorders

The following uncommon symptoms have occurred following abrupt treatment discontinuation or dose reduction: Nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, anxiety (see 4.4 Warnings and precautions).

Post-marketing adverse effects

The following adverse effects have been identified based on spontaneous post-marketing reports. Since the size of the population exposed is not known from these reports, it is not possible to reliably state their frequency.

Nervous system disorders: Serotonin syndrome, extrapyramidal symptoms (including akathisia and tardive dyskinesia).

Musculoskeletal disorders: Rhabdomyolysis (as a complication of neuroleptic malignant syndrome).

Reproductive system and breast disorders: Ejaculation failure, delayed ejaculation.

Investigations: Increased blood prolactin.

Class effect

Epidemiological studies, mainly conducted in patients aged 50 years and over, show an increased risk of bone fractures in patients receiving selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). The mechanism leading to this risk is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: /https://sideeffects.health.gov.il.

4.9. Overdose

Signs and symptoms

The initial signs and symptoms of Anafranil overdose are similar to those of other tricyclic antidepressants. The main complications are cardiac and neurological disorders. In children,

accidental ingestion of any amount of the product must be regarded as serious and potentially fatal.

Symptoms generally appear within 4 h of ingestion and reach maximum severity after 24 h. Owing to the delayed absorption (anticholinergic effect), long half-life and enterohepatic circulation of the medicinal product, the patient may be at risk for up to 4-6 days.

Rare cases of medication bezoars (masses of undigested or indigestible material) of varying severity, including fatal cases, have been reported in connection with overdoses of Anafranil sustained-release tablets. The medication bezoar may be radiopaque, enabling radiological (X-ray or CT scan) confirmation; however, this does not necessarily rule out this diagnosis. The formation of a medication bezoar may cause a slow but continual release and absorption of clomipramine, which may lead to overdose complications, including death, hours after taking the medicinal product and initial treatment with gastric lavage and active charcoal. Since gastric lavage may be ineffective and may even further increase systemic levels of the medicinal product, the physical removal of the medication bezoar by endoscopy or surgery should be considered in relevant selected patients. Since such cases are very rare, there is insufficient clinical data on optimum treatment, which should also take into account the size and location of the medication bezoar, patient symptoms and condition and medicinal product levels.

Central nervous system disorders: Somnolence, stupor, coma, ataxia, restlessness, agitation, hyperreflexia, muscle rigidity, choreoathetoid movements, convulsions. Symptoms possibly consistent with serotonin syndrome such as hyperpyrexia, myoclonus, delirium and coma have also been observed.

Cardiovascular disorders: Hypotension, tachycardia, arrhythmias, QTc prolongation, conduction disorders, shock, heart failure; very rare: cardiac arrest.

Respiratory depression, cyanosis, vomiting, fever, mydriasis, sweating, oliguria or anuria may also occur.

Treatment

No specific antidote is available. Treatment is essentially symptomatic and supportive.

In all cases of suspected Anafranil overdose, particularly in children, the patient must be hospitalised and kept under close surveillance for at least 72 h.

Primary decontamination with activated charcoal or by gastric lavage, within one hour of ingestion, is indicated for intoxication with high doses of non-sustained-release tricyclic antidepressants. In sustained-release medicinal products such measures should only be taken after clinical diagnostic assessment of the potential presence of a medication bezoar as – if a bezoar is present – an overdose may be exacerbated by the use of active charcoal and gastric lavage.

Due to the elevated risk of convulsions activated charcoal is preferable to gastric lavage. Patients with severe intoxication or reduced protective reflexes must first be intubated. The decontamination method of choice for sustained-release medicinal products is whole bowel irrigation with a polyethylene glycol electrolyte solution (e.g. Fordtran solution).

Repeated oral administration of activated charcoal may be effective for accelerated elimination (secondary decontamination) of some tricyclic antidepressants. Haemodialysis is not effective for secondary decontamination.

In patients with arterial hypotension, and/or ventricular arrhythmia with widening of the QRS complex in the ECG (>100 ms), treatment with sodium bicarbonate (1 mmol/kg) as a bolus injection or short infusion (5 min.) is indicated. This can be repeated until blood pressure increases and ECG changes improve, but only up to a maximum arterial pH of 7.55. Lidocaine may also be given i.v. Insertion of a temporary pacemaker is indicated in patients with bradyarrhythmia. In torsade de pointes-type polymorphic ventricular tachycardia: administration of a single i.v. injection of 0.5 to 1.5 g magnesium sulphate.

In patients with seizures: i.v. treatment with a benzodiazepine.

In patients with coma and/or respiratory failure: intubation and artificial respiration.

Hyperventilation may be used to raise arterial pH only if bicarbonate is not administered concurrently (risk of massive alkalosis).

Pyridostigmine and physostigmine are contraindicated for the treatment of peripheral and central anticholinergic symptoms due to their cardiac effects.

5. Properties/Actions

ATC code: N06AA04

Mechanism of action

The therapeutic effect of Anafranil is presumably based on its ability to inhibit neuronal reuptake of noradrenaline (NA) and serotonin (5-HT) released in the synaptic cleft, with inhibition of 5-HT reuptake being the more dominant component of this effect. Anafranil has alpha-1-adrenolytic, anticholinergic, antihistaminic and antiserotonergic (5-HT-2-receptor-blocking) properties.

5.1. Pharmacodynamics

Anafranil acts on the depressive syndrome, particularly characteristic features such as psychomotor inhibition, depressed mood and anxiety. The onset of action usually sets in after 2-3 weeks of treatment.

In addition to its antidepressant effect, Anafranil also has a specific effect in obsessive-compulsive disorders.

Clinical efficacy

No data available.

5.2. Pharmacokinetics

Absorption

Clomipramine is completely absorbed following oral administration. Clomipramine exhibits dose-proportional pharmacokinetics at doses between 25 and 150 mg.

The systemic bioavailability of unchanged clomipramine (CP) is reduced by about 50% due to hepatic first-pass metabolism to N-desmethylclomipramine (DMC, active metabolite).

Ingestion of food has no marked effect on clomipramine bioavailability. Only the onset of absorption may be slightly delayed, thereby prolonging the time to peak absorption. The coated tablets and sustained-release Divitabs are bioequivalent with respect to the amount absorbed.

A daily dose of 75 mg, administered either as one 25 mg coated tablet three times daily or as one 75 mg sustained-release Divitab daily, produces steady-state concentrations ranging from 20-175 ng/ml.

Steady-state concentrations of the active metabolite desmethylclomipramine follow a similar pattern. However, at a daily dose of 75 mg Anafranil, metabolite concentrations are 40-85% higher than those of clomipramine.

Distribution

Clomipramine is 97.6% bound to plasma proteins. The apparent volume of distribution is about 12-17 l/kg body weight. Concentrations in the cerebrospinal fluid are approximately 2% of the plasma concentration. Clomipramine is excreted in the breast milk at concentrations similar to those in plasma and crosses the placenta.

Metabolism

The primary route of clomipramine metabolism is demethylation to the active metabolite, N-desmethylclomipramine, which 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-N-desmethylclomipramine, the *in vivo* activity of which remains largely unknown. Clomipramine is also hydroxylated at the 2-position and N-desmethylclomipramine can be further demethylated to 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 metabolisers 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 h (range: 12-36 h) and desmethylclomipramine is eliminated with a mean half-life of 36 h.

About two thirds of a single dose of clomipramine is excreted in the form of water-soluble conjugates in the urine and 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 populations

Elderly patients: Irrespective of the dose, plasma concentrations of clomipramine are higher in elderly patients than in younger patients owing to reduced metabolic clearance.

Hepatic impairment: Clomipramine is metabolised by the enzymes CYP2D6, CYP3A4, CYP2C19 and CYP1A2.

5.3. Preclinical data

Chronic toxicity

Aspermatogenesis, testicular 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.

Mutagenicity

Clomipramine has not been adequately studied with respect to mutagenicity. Apart from negative *in vitro* findings, clomipramine displayed a mutagenic effect in studies in Drosophila. The relevance of these findings to clinical use is currently unknown.

Carcinogenicity

A 2-year, long-term study in rats yielded no evidence that clomipramine was carcinogenic.

Reproductive toxicity

No adverse effects on reproductive performance, including male and female fertility, were observed in rats at oral doses up to 24 mg/kg.

No teratogenic effects were observed in embryo-fetal development studies in animals. There was evidence of embryotoxicity in mice and rats (increased embryolethality).

Clomipramine, when administered prenatally and during the lactation phase, may cause behavioural disorders in the offspring.

6. Other information

6.1. List of excipients

Anafranil 25mg, coated tablets: Sucrose, Lactose monohydrate, Talc, Maize starch, Silica colloidal anhydrous, Stearic acid, Magnesium stearate, Glycerol 85%, Hypromellose, Vinylpyrrolidone, Povidone, Titanium dioxide (CI 77891, E 171), Titanium dioxide, Polyethylene glycol 8000, Cellulose microcrystalline, Iron oxide yellow (CI 77492, E 172).

Anafranil SR 75mg tablets: Calcium hydrogen phosphate dihydrate, Polyacrylate dispersion 30%, Calcium stearate, Hypromellose, Talc, Silica, colloidal anhydrous, Castor oil, hydrogenated, Pigment suspension white: Titanium dioxide (CI 77891, E171), Hypromelose (E464), Pigment suspension red: Iron oxide, red (CI 77491, E172), Hypromelose (E464).

6.2. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.3. Special precautions for storage

Store below 25°C.

Protect from moisture.

Keep out of the reach of children.

7. Registration holder and importer: Novartis Israel Ltd., P.O.B. 7126, Tel Aviv, Israel.

8. Registration numbers:

Anafranil 25 mg: 108-06-24600

Anafranil SR 75 mg tablets: 053-91-26407

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