1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

APHRODIL TABLETS (Clomipramine HCl Tablets 25 mg)

2. Qualitative and quantitative composition

2.1 Label Claim

Each film coated tablet contains:
Clomipramine HCl BP 25 mg
Excipients q.s.
Colour: Approved colours used

2.2 Quantitative Composition

Batch Size: 11.50 Lac Capsules

Sr. No.	Ingredients	Claim	Spec.	Qty/Tab (mg)	(%) Overages	Qty./11.50 Lac Tablets (Kg)
	Dry Mixing					
1.	Starch	----	BP	54.00	NIL	62.100
2.	Microcrystalline Cellulose	----	BP	22.00	NIL	25.300
3.	Povidone	----	BP	2.00	NIL	2.300
	Binders					
4.	Purified Water	----	BP	0.022 ml	NIL	25.3
5.	Methyl Hydroxy Benzoate	----	BP	0.10	NIL	0.115
6.	Propyl Hydroxy Benzoate	----	BP	0.02	NIL	0.023
7.	Starch	----	BP	2.17	NIL	2.500
	Lubricants					
8.	Clomipramine Hydrochloride	25 mg	BP	25.50	2 %	29.325
9.	Purified Talc	----	BP	2.00	NIL	2.300
10.	Magnesium Stearate	----	BP	1.00	NIL	1.150
11.	Croscarmellose Sodium	----	BP	1.00	NIL	1.150
12.	Colloidal Anhydrous Silica	----	BP	0.50	NIL	0.575
Average weight / weight of material in kg kg				**110 mg**		**126.838**
13.	Hydroxypropylmethylcellulose	----	BP	1.00	NIL	1.500

14.	Isopropyl Alcohol	----	BP	0.02 ml	NIL	23 liters
15.	Dichloromethane	----	BP	0.02 ml	NIL	23 liters
16.	Purified Talc	----	BP	0.60	NIL	0.690
17.	Titanium Dioxide	----	BP	0.60	NIL	0.690
18.	Propylene Glycol	----	BP	0.0002 ml	NIL	0.230
19.	P.E.G. - 400	----	BP	0.0002 ml	NIL	0.230
20.	Average weight of film coated tablet		112 mg			130.178 kg

3. Pharmaceutical form

Film coated tablet.

White coloured, circular, deep, biconvex, film coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

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 APHRODIL

TABLETS 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 APHRODIL TABLETS in children and adolescents (0-17 years of age) in these indications is therefore not recommended.

4.2 Posology and method of administration

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.

Children and adolescents

Adolescents generally show a stronger response to APHRODIL TABLETS than patients of intermediate age groups, APHRODIL TABLETS 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 treatment within 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

APHRODIL TABLETS should be given with caution in patients with renal impairment.

Hepatic impairment

APHRODIL TABLETS should be given with caution in patients with hepatic impairment.

Method of administration

APHRODIL TABLETS can be administered with or without food.

4.3 Contraindications

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

APHRODIL TABLETS must not be given in combination, or within 14 days before or after treatment, with a MAO inhibitor. The concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated.

Recent myocardial infarction.

4.3 Special warnings and precautions for use

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 APHRODIL TABLETS for any indication should be observed closely for clinical worsening, suicidality and other psychiatric symptoms 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 nonpsychiatric indications, should be alerted about the need to monitor patients for the emergence of other psychiatric symptoms, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers.

Prescriptions for APHRODIL TABLETS should be written for the smallest quantity of tablets or capsules consistent with good patient management, in order to reduce the risk of overdose. APHRODIL TABLETS 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 APHRODIL TABLETS. 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 APHRODIL TABLETS or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with APHRODIL TABLETS 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

APHRODIL TABLETS 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 supratherapeutic 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. 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 APHRODIL TABLETS.

Before starting treatment with APHRODIL TABLETS, 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. 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 APHRODIL TABLETS 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 the occurrence of seizures is dose dependent. Therefore, the recommended total daily dose of APHRODIL TABLETS should not be exceeded.

Like related tricyclic antidepressants, APHRODIL TABLETS should be given with electroconvulsive therapy only under careful supervision.

Anticholinergic effects

Because of its anticholinergic properties, APHRODIL TABLETS 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 APHRODIL TABLETS 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 APHRODIL TABLETS.

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 symptom.

4.4 Interaction with other medicinal products and other forms of interaction

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 APHRODIL TABLETS 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 APHRODIL TABLETS. In both instances APHRODIL TABLETS or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored.

There is evidence to suggest that APHRODIL TABLETS 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 APHRODIL TABLETS 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 APHRODIL TABLETS.

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). In addition comedication with SSRIs may lead to additive effects on the serotonergic system.

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.

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 APHRODIL TABLETS

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 APHRODIL TABLETS 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 APHRODIL TABLETS may be necessary when co-administered with terbinafine.

Cimetidine

Co-administration with the histamine2 (H2)-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 APHRODIL TABLETS (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 APHRODIL TABLETS with grapefruit, grapefruit juice, or cranberry juice may increase the plasma concentrations of clomipramine.

Interactions resulting in decreased effect of APHRODIL TABLETS

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 APHRODIL TABLETS.

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 APHRODIL TABLETS.

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 Ndesmethylclomipramine).

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 APHRODIL TABLETS 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

APHRODIL TABLETS 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 betablockers).

CNS depressants

Tricyclic antidepressants may potentiate the effects of alcohol and other central depressant substances (e.g. barbiturates, benzodiazepines, or general anesthetics).

Sympathomimetic drugs

APHRODIL TABLETS 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.

4.5 Pregnancy and lactation

Women of child-bearing potential

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

Pregnancy

Experience with APHRODIL TABLETS 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 APHRODIL TABLETS 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, APHRODIL TABLETS 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, APHRODIL TABLETS should be gradually withdrawn or the infant weaned if the patient is breast-feeding.

4.6 Effects on ability to drive and use machines

Patients receiving APHRODIL TABLETS 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. 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.

4.7 Undesirable effects

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, APHRODIL TABLETS 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.

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

4.8 Overdose

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 APHRODIL TABLETS, 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 APHRODIL TABLETS. Haemodialyses orperitoneal dialyses are ineffective because of the low plasma concentrations of clomipramine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The therapeutic activity of APHRODIL TABLETS 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.

APHRODIL TABLETS also has a wide pharmacological spectrum of action, which includes alpha1- adrenolytic, anticholinergic, antihistaminic, and anti-serotonergic (5-HT-receptor blocking) properties.

Pharmacodynamic effects

APHRODIL TABLETS 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.

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

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

5.3Pharmacokinetic 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 APHRODIL TABLETS, 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 APHRODIL TABLETS 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 Ndesmethylclomipramine

are hydroxylated to form 8-hydroxyclomipramine or 8-hydroxy-Ndesmethylclomipramine. 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.

5.3 Preclinical safety data

CLINICAL STUDIES

No recent clinical trials have been conducted with APHRODIL TABLETS.

NON-CLINICAL SAFETY DATA

According to the experimental data available, APHRODIL TABLETS has no mutagenic, carcinogenic or teratogenic effects. However, APHRODIL TABLETS 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.

6 Pharmaceutical particulars

6.1 List of excipients

Starch BP. Microcrystalline Cellulose BP, Povidone BP, Purified Water BP, Methyl Hydroxy Benzoate BP, Propyl Hydroxy Benzoate BP, Starch BP, Purified Talc BP, Magnesium Stearate BP, Croscarmellose Sodium BP, Colloidal Anhydrous Silica BP, Hydroxy propyl methyl Cellulose BP, Isopropyl Alcohol BP, Dichloromethane BP, Titanium Dioxide BP, Propylene Glycol BP, P.E.G.- 400 BP.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Keep out of reach of children Protect from light.
Store in a cool, &y and dark place.

6.5 Nature and contents of container

3 x 10 Capsules Blister pack along with leaflet in one carton.

6.6 Special precautions for disposal and other handling

None stated.

7 Manufactured by

Hab Pharmaceuticals & Research Ltd.,

10, Pharmacity,
Selaqui, Dehradun,
Uttarakhand - 248011,
India.

8 Marketing authorisation holder

Hab Pharmaceuticals & Research Ltd.,
10, Pharmacity,
Selaqui, Dehradun,
Uttarakhand - 248011,
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