SUMMARY OF PRODUCT CHARACTERISTICS

ORMAL TABLETS

1. TRADE NAME OF THE MEDICAL PRODUCT

ORMAL 25

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ORMAL 25: Amitriptyline HCl (25.0mg), Lactose (34.81mg), Microcrystalline cellulose (88.89mg), Sodium starch glycolate (11.85mg), Sodium lauryl sulfate (0.926mg), Colloidal silicon dioxide (1.11mg), Magnesium stearate (3.185 mg), Talc (3.70mg), sunset yellow (0.519mg).

3. PHARMACEUTICAL FORM

TABLETS

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For use in the symptoms of depressive illness especially where sedation is required.

4.2. Posology and method of administration

For oral use.

Adults and adolescents over 16 years old

Initially 50-100mg as a single dose at night, increasing to 200mg/day according to clinical response. Once a satisfactory response has been obtained, the dosage should be reduced to the lowest dose that will maintain the symptomatic benefit. The usual maintenance dose is 50-100mg as a single dose at night.

Elderly (over 65 years)

Initially 25-75mg a day. Since the elderly are particularly prone to experience adverse effects such as agitation, confusion and postural hypotension; the initial dose should only be increased with caution under close medical supervision. Half the normal maintenance dose may be sufficient to produce a satisfactory clinical response.

Children (under 16 years)

Not recommended.

4.3. Contraindications

Recent cardiac infarction and patients with any degree of heart block or disorders of cardiac rhythm and those suffering from coronary artery insufficiency. Patients with mania, severe liver disease, or known hypersensitivity to dibenzepines. Co-administration with monoamine oxidase inhibitors. Lactation. Porphyria.

4.4. Special warnings and special precautions for use

As improvement may not occur during the first 2-4 weeks of treatment, patients should be closely monitored during this period especially those posing a high suicidal risk.

Cardiac arrhythmias and severe hypotension are likely to occur with high dosage or in deliberate overdosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

Unless essential it is inadvisable to combine Amitriptyline-HCl and ECT.

When Amitriptyline-HCl is used for the depressive component of schizophrenia, psychotic symptoms may be aggravated. In manic depressives, a shift towards the manic phase may occur; paranoid delusions, with or without associated hostility, may be aggravated.

Avoid if possible in patients with a history of urinary retention, narrow angle glaucoma, impaired liver function, or increased ocular pressure, symptoms suggestive of prostatic hypertrophy and a history of epilepsy. Amitriptyline-HCl should be used with caution in hyperthyroid patients.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue Amitriptyline-HCl several days before surgery; if emergency surgery is unavoidable, the anesthetist should be informed that the patient is being so treated.

Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic or with neuroleptic medications.

Abrupt withdrawal of Amitriptyline-HCl should be avoided.

Suicide/suicidal thoughts or clinical worsening:

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Other psychiatric conditions for which amitriptryptiline is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

4.5. Interaction with other medicaments and other forms of interaction

Amitriptyline-HCl should not be administered concurrently, or within 14 days of termination of treatment with MAO inhibitors. It should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine, and should be used with caution when administered concurrently with anticholinergic drugs or thyroid medications.

Based on the known metabolism of amitriptyline, the protease inhibitor, ritonavir, may increase the serum levels of amitriptyline. Therefore careful monitoring of therapeutic and adverse effects is recommended when these drugs are administered concomitantly.

Amitriptyline-HCl may counteract the effect of adrenergic neurone blocking agents, and possibly clonidine, and therefore it would be advisable to review all anti-hypertensive therapy during treatment.

The action of Amitriptyline-HCl may be decreased by barbiturates and potentiated by methylphenidate. Amitriptyline-HCl may enhance the response to alcohol, barbiturates and other CNS depressants.

Cimetidine is reported to reduce hepatic metabolism of certain tricycli antidepressants. Delirium has been reported in patients taking amitriptyline with disulfiram.

4.6. Pregnancy and lactation

Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons. There is no, or inadequate, evidence of safety of the drug in human pregnancy. There is evidence of harmful effects in pregnancy in animals, when given in exceptionally high doses.

Adverse effects such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers had taken amitriptyline during the last trimester of pregnancy.

Amitriptyline is detectable in breast milk. Because of the potential for serious adverse reactions in infants from amitriptyline, Amitriptyline-HCl should not be given to mother during breast-feeding. A decision should be made whether to discontinue breast-feeding or discontinue the drug.

4.7. Effects on ability to drive and use machines

Amitriptyline may initially impair alertness and also potentiate ate the CNS depressant effects of alcohol. Patients should be warned of the possible hazard when driving or operating machinery. This can usually be controlled by reducing the dose. If necessary the dose can be subsequently increased gradually.

4.8. Undesirable effects

The following adverse effects, although not necessarily all reported with amitriptyline, have occurred with tricyclic antidepressants.

Anticholinergic: Excessive perspiration, dryness of mouth, blurred vision, mydriasis, disturbed accommodation, increased intraocular pressure, hyperpyrexia, urinary retention and urinary tract dilatation. These symptoms are common but usually lessen on continuing therapy.

Cardiovascular Reactions: Hypotension, syncope, postural hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke, non-specific ECG and AV conduction changes.

CNS and Neuromuscular: Confusional states, disturbed concentration, disorientation, delusions, hallucinations, hypomania, excitement, anxiety, restlessness, drowsiness, insomnia, nightmares, numbness, tingling and paraesthesia of the extremities, peripheral neuropathy, incoordination, ataxia, tremors, coma, convulsions, alteration of EEG, extrapyramidal symptoms including abnormal involuntary movements, and tardive dyskinesia, dysarthria, tinnitus, dizziness, weakness, fatigue, headache.

Allergic: Skin rash, urticaria, photosensitisation, oedema of face and tongue.

Haematological: Bone-marrow depression including agranulocytosis, leucopenia, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, unpleasant taste, diarrhoea, weight loss, increased appetite and weight gain (may be a drug reaction or due to relief of the depression), parotid swelling, black tongue, rarely hepatitis (including altered liver function and cholestatic jaundice), constipation, paralytic ileus.

Endocrine: Testicular swelling, gynaecomastia, breast enlargement, galactorrhoea, increased or decreased libido, impotence, interference with sexual function, elevation or lowering of blood sugar levels, inappropriate ADH (antidiuretic hormone) secretion.

Cases of suicidal ideation and suicidal behaviours have been reported during amitriptyline therapy or early after treatment discontinuation (see section 4.4).

Withdrawal symptoms may occur on abrupt cessation of therapy and include insomnia, irritability, nausea, headache and excessive perspiration.

Mania or hypomania has been reported rarely within 2-7 day of stopping chronic therapy with tricyclic antidepressants.

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Formatted: Justified, Line spacing: 1.5 lines

Formatted: Font: (Default) Arial, 11 pt, English (U.K.)

Formatted: Font: (Default) Arial, 11 pt, English (U.K.)

4.9 Overdose

Amitriptyline exerts an anticholinergic effect as well as antihistamine and adrenaline blocking actions. Large doses produce temporary confusion, disturbed concentration, transient visual hallucinations, drowsiness, hypothermia convulsions, coma, apnoea, tachycardia and other rhythm dysfunctions such as bundle branch block; ECG evidence of impaired conduction, congestive heart failure, dilated pupils, disorders of ocular motility, severe hypotension, stupor, polyradiculoneuropathy and intestinal stasis.

Other symptoms may be agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia, or any of those listed as adverse effects.

Treatment: Gastric lavage and emesis if appropriate. Following lavage, activated charcoal may be given during the first 24-48 hours at a dosage of 20-30g every four to six hours. Vital signs should be continuously monitored and patients should be treated in hospital wherever possible. General supportive measures should be initiated with careful attention to electrolyte balance. An ECG should be taken and close monitoring of cardiac function instituted if there is any sign of abnormality. Cardiac irregularities may need controlling with antiarrhythmic drugs and physostigmine salicylate may be indicated. If convulsions occur. Paraldehyde, diazepam or inhalation anaesthetics, but not barbiturates, may be indicated. Forced diuresis and haemodialysis have no place in treatment. An open airway and an adequate fluid intake should be maintained and body temperature regulated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Amitriptyline is a tricylic antidepressant. It prevents reuptake and hence inactivation of noradrenaline and serotonin at nerve terminals. The precise mechanism by which an antidepressant effect is achieved remains unclear.

5.2. Pharmacokinetic properties:

After release from Amitriptyline-HCl Capsules, amitriptyline is readily absorbed from the gastrointestinal tract. Peak serum levels are reached between 6 and 12 hours after administration of Amitriptyline-HCl.

Amitriptyline is extensively demethylated in the liver to its primary active metabolite, nortriptyline. Paths of metabolism of both amitriptyline and nortriptyline include hydroxylation (possibly to active metabolites), N-oxidation and conjugation with glucuronic acid. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, ether free or in conjugated form. Amitriptyline and nortriptyline are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Amitriptyline has been estimated to have a half-life ranging from 9 to 25 hours, which may be considerably extended in overdosage. Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and simple correlation with therapeutic

response has not been established. Amitriptyline and nortriptyline cross the placental barrier and are excreted in breast milk.

5.3. Preclinical safety data

Preclinical safety data does not add anything of further significance to the prescriber.

6. Pharmaceutical information

6.1 List of excipients

Amitriptyline HCl, Lactose, Microcrystalline cellulose, Sodium starch glycolate, Sodium lauryl sulfate, Colloidal silicon dioxide, Magnesium stearate, Talc, Sunset yellow.

6.2 Incompatibilities:

Not applicable

6.3 Shelf-life:

60 months

6.4 Special precautions for storage:

Store at 25°C, protected from light and humidity.

6.5 Nature and contents of container:

Al/PVC blister strips

6.6 Instructions for use/handling:

None

7. Marketing authorization holder

AEGIS LTD, ERGATES INDUSTRIAL AREA,
P.O. BOX 28629, 2081 NICOSIA, CYPRUS, EUROPE

8. Marketing authorization number: ORMAL 25: 18055

9. Date of first authorization/renewal of authorization: 30/11/1998

10. Date of (partial) revision of the text: May 2010