

AMITRIPTYLINE 25MG TABLETS BP

PL 15755/0028

UKPAR

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AMITRIPTYLINE 25MG TABLETS BP

PL 15755/0028

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted OBG Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Amitriptyline 25mg Tablets BP (PL 15755/0028). This prescription only medicine (POM) is an antidepressant, indicated for the treatment of symptoms of depressive illness, especially when sedation is required, and for night-time bedwetting.

Amitriptyline 25mg Tablets BP contain the active ingredient Amitriptyline Hydrochloride, an antidepressant with sedative properties.

This application is based on the reference product Amitriptyline Tablets BP 25mg (PL 00790/0054), which was first granted a UK licence on 23rd May 1985.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Amitriptyline 25mg Tablets BP outweigh the risks, hence a Marketing Authorisation has been granted.

AMITRIPTYLINE 25MG TABLETS BP

PL 15755/0028

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisation for the medicinal product Amitriptyline 25mg Tablets BP (PL 15755/0028) to OBG Pharmaceuticals Limited on 10 February 2006. This product is a POM.

The application was submitted as an abridged application according to article 4.8 (a) (i) of Directive 65/65/EEC, cross-referring to Amitriptyline Tablets BP 25mg (PL 00790/0054), approved on 23 May 1985.

No new data was submitted, nor was it necessary for this simple application, as the data is identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.

PHARMACEUTICAL ASSESSMENT REPORT

INTRODUCTION AND BACKGROUND

This is a simple, piggyback application for a single strength of amitriptyline tablets, submitted under Article 4.8 (a) (i) of Directive 65/65/EEC. The cross-reference MA is Amitriptyline Tablets BP 25mg (PL 00790/0054) held by Clonmel Healthcare Ltd., which was granted on 23rd May 1985.

A letter of consent from Clonmel Healthcare has been included as part of the application and refers to the correct cross-reference product. OBG Pharmaceuticals has confirmed that it has access to all of the relevant data.

Amitriptyline is a tricyclic antidepressant, indicated for the treatment of symptoms of depressive illness, especially when sedation is required, and for nocturnal enuresis.

EXPERT REPORT

The Pharmaceutical Expert Statement was prepared by a suitably qualified pharmacist, whose CV has been provided, and confirms that the product is identical in all qualitative and quantitative particulars to the cross-reference product.

The Pharmacotoxicological and Clinical Expert Statements were prepared by a medically qualified doctor. A CV has been provided and is satisfactory.

MARKETING AUTHORISATION APPLICATION (MAA)

ACTIVE INGREDIENT SOURCE

The active substance is obtained from three sources that are the same as for the cross-reference product.

Drug substance specifications have been provided from all of the active substance suppliers. These all meet the requirements of the Ph. Eur. monograph for amitriptyline hydrochloride, some of the limits being tighter than specified in the monograph. Supplier-specific tests are also given. These are acceptable.

MANUFACTURER

The finished product manufacturer is Clonmel Healthcare Ltd, Tipperary, Ireland and this is also the company responsible for batch release in the EEA. A copy of their Manufacturing Authorisation has been provided as part of this application. This is the same as for the cross-reference product and is satisfactory. A letter confirming their willingness to manufacture the product on behalf of the applicant has been provided.

No flow-chart of sites involved in manufacture is necessary, since all functions are carried out at the same site.

MANUFACTURING PROCESS

The composition of the sugar-coated tablets is identical to that of the cross-reference product and the manufacturing process is identical to that of the cross-reference product.

PRODUCT SPECIFICATIONS

The finished product specification provided is identical to that of the cross-reference product. It is consistent with the requirements of the BP monograph for Amitriptyline tablets and the Ph. Eur. monograph on Amitriptyline tablets. This is acceptable.

STORAGE DETAILS

The proposed shelf life is 36 months, with the storage conditions: "Do not store above 25°C. Store in the original container. Keep the container tightly closed." The shelf life is identical to that approved for the cross-reference product. The storage conditions are also the same, but have had their wording updated to the standard terms. This is acceptable.

PACKAGING

The proposed packaging is identical to that of the cross-reference product.

PACK SIZES

The proposed pack sizes are of 50, 100, 250 and 500 tablets. These are the same as for the cross-reference product and are, therefore, acceptable.

TSE COMPLIANCE

Two of the excipients have been specified as coming from animal sources: lactose and magnesium stearate. A Ph. Eur. certificate of suitability has been provided for magnesium stearate from its supplier and is satisfactory.

Declarations from the suppliers of lactose monohydrate, confirming compliance with the Biotechnology Working Party Public report of May 2002 have been provided.

OTHER INFORMATION

A suitably qualified person has been nominated to take responsibility for pharmacovigilance. A CV has been provided. This is acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is virtually identical to that of the cross-reference product and is satisfactory.

LEAFLET AND LABELLING

The leaflet and label mock-ups provided are satisfactory.

CONCLUSION

There are no objections to the granting of a Marketing Authorisation.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none is required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. The risk benefit ratio is considered to be positive.

AMITRIPTYLINE 25MG TABLETS BP

PL 15755/0028

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 1 February 2002
2	Following assessment of the application the MHRA requested further information relating to the quality dossier on 18 March 2002
3	The applicant responded to the MHRA's requests, providing further information on 7 October 2004
4	Following assessment of the response the MHRA requested further information relating to the quality dossier on 17 November 2004
5	The applicant responded to the MHRA's requests, providing further information on 9 September 2005
6	Following assessment of the response the MHRA requested further information relating to the quality dossier on 9 September 2005
7	The applicant responded to the MHRA's requests, providing further information on 15 December 2005
8	The application was determined on 10 February 2006

Product Summary for Amitriptyline 25mg Tablets BP (PL 15755/0028):

1. NAME OF THE MEDICINAL PRODUCT

Amitriptyline 25mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of Amitriptyline Hydrochloride

For excipients see 6.1

3. PHARMACEUTICAL FORM

Coated tablet

Appearance

Pale yellow, circular, biconvex, sugar coated tablets.

4. CLINICAL PARTICULARS

4.1 *Therapeutic indications*

Amitriptyline is an anti-depressant of the tricyclic group.

It is indicated for symptoms of a depressive illness especially when sedation is required.

Amitriptyline is also effective in nocturnal enuresis where organic pathology is excluded.

4.2 *Posology and method of administration*

Route of administration: Oral

Adults:

Initial Dose: Usually 75mg daily in divided doses, or as a single dose at night. This may be increased, if required, to a total of 150mg daily, the additional doses being given in the late afternoon and/or at bedtime. Although the sedative effect is usually achieved rapidly, the antidepressant activity may not be apparent for three or four days and may take up to 30 days to develop adequately.

Maintenance dosage: Usually 50 to 100mg daily and the total dosage may be taken as a single dose, preferably in the evening or at bedtime. When satisfactory improvement has been achieved, dosage should be reduced to the lowest amount necessary to maintain control of symptoms. Maintenance therapy should be continued for at least three months in order to reduce the possibility of relapse.

Elderly:

In general, lower doses are recommended for elderly patients and an initial dose of 10-25 mg t.d.s is recommended which should be increased slowly if required. A daily dosage of 50mg may be satisfactory in elderly patients who may not tolerate higher dosages. The required dosage may be administered either as divided doses or as a single dose preferably in the evenings or at bedtime.

Children

Not recommended for treatment of depression in children under 16 years of age due to a lack of clinical experience.

Enuresis: Children aged 11 to 16 years may receive 25 to 50 mg a day. This product is unsuitable for use in children under 10 years of age. Treatment should not exceed three months.

4.3 Contraindications

Co-administration with monoamine oxidase inhibitors; prior sensitisation to amitriptyline; during the recovery phase after myocardial infarction; arrhythmias, particularly heartblock of any degree; mania; severe liver disease; lactation; children under 6 years of age; porphyria.

The concomitant use of tricyclic antidepressants with amiodarone or sibutramine.

4.4 Special warnings and precautions for use

General: Amitriptyline should be used with caution in patients with a history of epilepsy, in patients with impaired liver function and, because of its atropine-like action, in patients with a history of urinary retention, prostatic hypertrophy, narrow-angle glaucoma, or increased intra-ocular pressure. In patients with narrow-angle glaucoma, even average doses may precipitate an attack of glaucoma.

There has been a report of fatal dysrhythmia occurring as late as 56 hours after amitriptyline overdose.

If possible, discontinue amitriptyline several days before surgery. But if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being treated with amitriptyline, because anaesthesia may increase the risk of hypotension and arrhythmias.

Hyperpyrexia has been reported when tricyclic anti-depressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Amitriptyline may impair alertness in some patients and activities made hazardous by diminished alertness (e.g. driving a car) should be avoided.

Elderly patients are particularly liable to experience adverse reactions: especially agitation, confusion and postural hypotension.

Cardiovascular/endocrine disorders: Patients with cardiovascular disorders, hyperthyroid patients, and those receiving thyroid medication or anticholinergic agents should be closely supervised and the dosage of all medications carefully adjusted.

Central nervous system disorders: When amitriptyline 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. In such cases, a major tranquilliser should be given concurrently, or the dosage of amitriptyline reduced.

The risk of suicide remains during treatment of depressed patients and until significant remission occurs. Such patients require careful supervision.

Use in children: Behavioural changes have been observed in children receiving tricyclics for the treatment of enuresis.

Unless essential it is inadvisable to combine amitriptyline and electroconvulsive therapy (ECT) [see section 4.5 “Interactions”].

Abrupt withdrawal of amitriptyline should be avoided (see section 4.8 “Undesirable Effects, Other reactions”).

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant (see section 4.8 “Undesirable Effects, Endocrine”).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Other antidepressant drugs: The concurrent use of antidepressants having varying modes of action should be made only with due recognition of their possible potentiation and with a thorough knowledge of their respective pharmacologies. Monoamine oxidase inhibitors can potentiate the effects of tricyclic antidepressants such as amitriptyline, and hyperpyretic crises, severe convulsions, and fatalities have occurred. A minimum of 14 days should elapse between discontinuing an MAOI and starting amitriptyline, which should be introduced cautiously and dosage increased gradually.

Antihypertensives: Amitriptyline may block the antihypertensive action of guanethidine, debrisoquine, betanidine, and possibly clonidine. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Anticholinergic agents/sympathomimetic drugs: Amitriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine.

Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with drugs having an anticholinergic action.

Central nervous system depressants: Amitriptyline may enhance the response to alcohol, barbiturates, and other CNS depressants. In turn, barbiturates may decrease, and methylphenidate may increase, the antidepressant action of amitriptyline. Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients treated with 1g ethchlorvynol and 75 mg to 150 mg of amitriptyline.

Disulfiram: Delirium has been reported in patients taking amitriptyline with disulfiram.

Cimetidine: Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants.

Electroconvulsive therapy: Concurrent administration with ECT may increase the hazards of treatment, and should be limited to patients for whom it is deemed essential.

Ritonavir: 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.

Altretamine: Concurrent administration of altretamine and tricyclic antidepressants may cause severe orthostatic hypotension.

Analgesics: Caution should be exercised when nefopam is administered concurrently with tricyclic antidepressants. Tramadol may increase the potential for tricyclic antidepressants to

cause convulsions. The concurrent administration of opioid analgesics with tricyclic antidepressants may lead to increased sedation.

Anti-arrhythmics: There is an increased risk of ventricular arrhythmias with drugs which prolong QT interval, including amiodarone (avoid concomitant use), disopyramide, procainamide, propafenone, quinidine and sotalol.

Rifampicin: The plasma concentration of some tricyclic antidepressants may be reduced by rifampicin.

Antiepileptics: Tricyclic antidepressants may precipitate seizures in susceptible patients and the dosage of antiepileptics may need to be adjusted. The plasma concentration of some tricyclic antidepressants may be reduced by antiepileptics.

Antipsychotics: There is an increased risk of ventricular arrhythmias if thioridazine or pimozide are taken concomitantly with tricyclic antidepressants. Concurrent administration with phenothiazines may lead to increased plasma concentrations of tricyclic antidepressants and increased antimuscarinic side effects.

Dopaminergics: The concomitant use of entacapone with tricyclic antidepressants is not recommended. Severe CNS toxicity has been reported in patients with the combination of tricyclic antidepressants and selegiline.

Baclofen: The use of baclofen and tricyclic antidepressants may result in the potentiation of the effect of baclofen, resulting in pronounced muscular hypotonia.

Nitrates: The effectiveness of sublingual and buccal tablet preparations may be reduced by drugs that cause dry mouth since dissolution may be delayed.

Oral contraceptives: Oral contraceptives antagonise the antidepressant effect of tricyclic antidepressants but may increase the side effects due to increased plasma concentrations of tricyclics.

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; although it has been in wide use for many years without apparent ill-consequence. There is evidence of harmful effects in pregnancy in animals, when given in exceptionally high doses.

Amitriptyline is detectable in breast milk. Because of the potential serious adverse reactions in infants from amitriptyline, 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. Patients should be warned of the possible hazard when driving or operating machinery.

4.8 Undesirable effects

Cardiovascular reactions: Hypotension, syncope, postural hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke, non-specific ECG changes and changes in AV conduction. Arrhythmias and severe hypotension are likely to occur with high dosage or overdose.

CNS and neuromuscular: Confusional states, disturbed concentration, disorientation, delusions, hallucinations, hypomania, excitement, anxiety, restlessness, drowsiness, insomnia,

nightmares, numbness, tingling, and paraesthesiae of the extremities, peripheral neuropathy, incoordination, ataxia, tremors, coma, convulsions, alteration of the EEG, extrapyramidal symptoms, including abnormal involuntary movements and tardive dyskinesia, dysarthria, tinnitus.

Anticholinergic: Dry mouth, blurred vision, mydriasis, disturbance of accommodation, increased intra-ocular pressure, constipation, paralytic ileus, hyperpyrexia, urinary retention, urinary tract dilatation.

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

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

Gastro-intestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, unpleasant taste, diarrhoea, parotid swelling, black tongue, rarely hepatitis (including altered liver function and 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, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other reactions: Dizziness, weakness, fatigue, headache, weight loss, oedema, increased perspiration, urinary frequency, alopecia, increased appetite and weight gain (may be a drug reaction or due to relief of the depression). Abrupt withdrawal after prolonged administration has caused nausea, headache and malaise. Reports have associated gradual withdrawal with transient symptoms including irritability, restlessness, as well as dream and sleep disturbances during the first two weeks of dosage reduction. These symptoms are not indicative of addiction.

Adverse reactions such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic anti-depressants in the last trimester of pregnancy.

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

Side effects in enuresis: Dosages used in enuresis are low compared with those used in depression, and side effects are therefore less frequent. The most common are drowsiness and anticholinergic effects. The only other side effects, reported infrequently at these dosages, have been mild sweating and itching.

The recommended dosage must not be exceeded.

Side effects - causal relationship unknown: The following additional side-effects have been reported; however, a causal relationship to therapy with amitriptyline has not been established: lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

4.9 Overdose

High doses of amitriptyline may cause temporary confusion, disturbed concentration, or transient visual hallucinations.

Overdosage may cause hypothermia; drowsiness; tachycardia and other arrhythmic abnormalities such as bundle branch block; congestive heart failure; ECG evidence of impaired conduction; dilated pupils; disorders of ocular motility, convulsions; severe hypotension; stupor, coma and polyadiculoneuropathy; constipation.

Other symptoms which may occur include agitation, muscle rigidity, hyperactive reflexes, hyperpyrexia, vomiting or any of the effects listed in the section on undesirable effects above.

All persons suspected of having taken an overdose should be admitted to hospital as soon as possible. Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible by emesis, followed by gastric lavage once in hospital.

Following gastric lavage, oral administration of activated charcoal during the first 24 - 48 hours at a dosage of 20 - 30 g every four to six hours has been shown to reduce the delayed toxic effects due to enterohepatic circulation and slow absorption. An ECG should be taken and the cardiac function should be monitored closely if there is any sign of abnormality. An open airway and an adequate fluid intake should be maintained; body temperature should be regulated.

Physostigmine salicylate, 1-3 mg, given intravenously has been reported to reverse the symptoms of tricyclic antidepressant poisoning. Because of the rapid metabolism of physostigmine, the dosage of physostigmine should be repeated as required, particularly if life-threatening signs such as convulsions, arrhythmias and deep coma recur or persist after the initial dose of physostigmine. Because physostigmine may itself be toxic, it is not recommended for routine use.

Standard measures should be employed to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine or propranolol. If cardiac failure occurs, use of digitalis should be considered. It is advisable to closely monitor cardiac function for at least five days.

If convulsions occur, they should be treated with paraldehyde, diazepam or an inhalation anaesthetic. Barbiturates should not be used because amitriptyline increases their CNS-depressant action.

Dialysis is of no value in amitriptyline overdose because of the low plasma concentrations of amitriptyline. Since overdose is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdose have occurred with tricyclic antidepressants.

5. PHARMACOLOGICAL PROPERTIES

5.1 *Pharmacodynamic properties*

ATC Code: N06A A09

Amitriptyline is a tricyclic antidepressant. It has marked antimuscarinic and sedative properties, and prevents the re-uptake (and hence the inactivation) of noradrenaline and serotonin at nerve terminals. Its mode of action in depression is not fully understood. Amitriptyline is used in the treatment of depression, particularly endogenous depression.

5.2 *Pharmacokinetic properties*

Amitriptyline is readily absorbed from the gastro-intestinal tract, peak plasma concentration occurring within about 6 hours of oral administration. 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) and N-oxidation. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either 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.

5.3 *Preclinical safety data*

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 *List of excipients*

Lactose monohydrate, povidone, magnesium stearate, stearic acid, maize starch.

Sugar-coat excipients: polyvinylacetate phthalate, stearic acid, talc, calcium carbonate, acacia, titanium dioxide, sucrose, povidone, quinoline yellow aluminium lake, sunset yellow aluminium lake, sodium benzoate, shellac, yellow carnauba wax, white beeswax.

6.2 *Incompatibilities*

Not applicable

6.3 *Shelf life*

3 years

6.4 *Special precautions for storage*

Do not store above 25°C. Store in the original container. Keep the container tightly closed.

6.5 *Nature and contents of container*

Polypropylene tablet containers with low density polyethylene caps.
Packing material: High density polyethylene film.
Pack size: 50, 100, 250 and 500 tablets.

6.6 *Special precautions for disposal*

Not applicable.

7. MARKETING AUTHORISATION HOLDER

OBG Pharmaceuticals Ltd.
Reeds Lane
Moreton
Wirral
CH46 1DW

8. MARKETING AUTHORISATION NUMBER(S)

PL 15755/0028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/02/2006

10. DATE OF REVISION OF THE TEXT

10/02/2006

PATIENT INFORMATION LEAFLET

Amitriptyline 25 mg Tablets BP

This leaflet provides a summary of the information available on your medicine; please read it carefully before you start to take your medicine. If you have any questions or are not sure of anything ask your doctor or pharmacist.

What is in this medicine?

Amitriptyline 25 mg tablets are pale yellow, circular, sugar coated tablets. Each tablet contains amitriptyline hydrochloride 25 mg, the active ingredient.

The tablets also contain the inactive ingredients lactose monohydrate, maize starch, povidone, magnesium stearate, stearic acid, calcium carbonate, talc, acacia, sucrose, polyvinylacetate phthalate, yellow carnauba wax, white beeswax, shellac and the colours titanium dioxide, quinoline yellow aluminium lake (E104) and sunset yellow aluminium lake. The sugar coat contains the preservative sodium benzoate (E211).

Pack sizes: 50, 100, 250 and 500 tablets.

What is amitriptyline?

Amitriptyline belongs to a group of drugs called tricyclic antidepressants (TCADs). It prolongs the effects of noradrenaline and serotonin (substances which transmit nerve impulses).

MA holder:

OBG Pharmaceuticals Ltd, Reeds Lane, Moreton, Wirrel CH46 1DW.

Manufacturer:

Clonmel Healthcare Ltd, Waterford Road, Clonmel, Co Tipperary, Ireland.

What is this medicine for?

Amitriptyline is used to treat depression. It is also used to treat night bedwetting in children.

What do you need to know before taking this medicine?

If the answer to any of the following questions is YES, DO NOT take this medicine without consulting your doctor.

- Have you previously suffered an allergic reaction to a medicine containing amitriptyline or other anti-depressant medicines?
- Are you allergic to any of the other ingredients? (See 'What is in this medicine?' above)
- Do you suffer from any liver or heart problems (e.g. abnormal heart rhythm)?
- Have you had glaucoma (increased pressure in the eyes)?
- Do you have difficulty in passing water?

- Have you suffered a heart attack within the last three months?
- Are you taking or have you recently taken (within the last 14 days) any other medicines for depression, particularly monoamine oxidase inhibitors (MAOIs)?
- Are you pregnant, trying to become pregnant, or breast-feeding?
- Do you have a history of epilepsy or suffered recently from convulsions?
- Do you have an overactive thyroid gland?
- Do you suffer from any mental illness other than depression?
- Have you had prostate trouble?
- Do you have porphyria?

If you feel dizzy or drowsy when you start taking this medicine, do not drive or operate machinery until these effects wear off.

If you are to undergo any surgery or receive anaesthetics (even at the dentist) or have electroconvulsive therapy (ECT), you should make the doctor or dentist treating you aware that you are taking amitriptyline.

If you experience symptoms such as drowsiness, confusion or fits, tell your doctor immediately because this may indicate a low sodium level in the blood.

Are you taking any other medicines?

You should consult your doctor BEFORE taking any other medicines, including:

- Other medicines used to treat depression including monoamine oxidase inhibitors (MAOIs)
- Medicines used to lower blood pressure (e.g. guanethine, debrisoquine, bethanidine, methyl dopa, and clonidine)
- Drugs that depress the central nervous system including barbiturates (e.g. phenobarbitone)
- Methylphenidate, a drug used to treat sleeping problems
- Sedatives (medicines that relieve anxiety and have a calming effect)
- Thyroid hormone therapy
- Medicines used to treat Parkinson's disease, including entacapone and selegiline
- Disulfiram (a medicine used to treat alcoholism)
- Cimetidine (a medicine used to treat ulcers)
- Medicines used to relieve: asthma, gastrointestinal upset (e.g. vomiting or cramps) and allergies (antihistamines)
- Medicines such as adrenaline, ephedrine, phenylephrine, or phenylpropanolamine. These may be present in many medicines for colds and nasal stuffiness. Tell your pharmacist that you are taking amitriptyline before buying such products
- Ritonovir, a drug used for HIV infection
- Sibutramine, a medicine used for weight loss
- Altretamine, a drug used for the treatment of advanced ovarian cancer
- Certain painkillers, including nefopam and tramadol
- Medicines used to treat irregular heart rhythm, including amiodarone, disopyramide, procainamide, propafenone, quinidine and sotalol
- Rifampicin (an antibiotic)

- Medicines used to treat epilepsy
- Medicines used to treat mental illnesses, including thioridazine and pimozide
- Baclofen, a drug used for muscle spasm resulting from disorders such as multiple sclerosis
- Medicines used in the treatment of angina
- Oral contraceptives.

Avoid alcohol while taking this medicine as it may affect you more than usual.

What else do you need to know?

If your doctor has told you that you have an intolerance to some sugars, contact your doctor before taking this medicine.

The tablets contain sunset yellow colour which may cause allergic reactions.

How much of this medicine should you take?

You should take your medicine as directed by your doctor. The pharmacist's label should tell you how much to take and how often. If it does not or you are not sure ask your doctor or pharmacist.

Adults: The usual dose is one tablet 3 times daily or alternatively three tablets at bedtime. If necessary, your doctor may increase the dose to a total of 150 mg (6 tablets) per day. Maintenance dose: Usually 50 – 100 mg per day, taken as a single dose in the evening or at bedtime.

Elderly: Lower doses are generally recommended for elderly patients. An initial dose of 10 – 25 mg three times daily which should be increased slowly if required.

Children (for night bedwetting): 11 – 16 years: 25 – 50 mg per day. This product is unsuitable for children under 10 years of age.

Treatment should not exceed three months.

Not recommended for treatment of depression in children under 16 years of age.

- Amitriptyline tablets are not suitable for children under 6 years.
- The tablets should be swallowed with a drink of water.
- This medicine should only be used for up to 3 months to treat night bedwetting.
- If you are elderly you will be advised by your doctor specifically on how many and how often to take the tablets.
- This medicine is not suitable for the treatment of depression in children under 12 years.
- You should keep taking your medicine until your doctor tells you to stop. This medicine may take up to four weeks to be fully effective.
- Do not stop taking your medicine suddenly, unless your doctor tells you to, as this may lead to unwanted effects such as nausea, headache or weakness.

What if you have taken too many tablets?

If you or anyone else has swallowed a lot of the tablets all together contact your nearest hospital casualty department or doctor immediately.

If you forget to take a dose, take the next dose at the usual time. Do not take two doses together.

What unwanted effects can this medicine have?

This medicine, like most other medicines, may cause side effects in some people. If you experience any of the following tell your doctor IMMEDIATELY.

- Palpitations or an unusually rapid heart beat
- Dizziness or fainting when you stand up
- Development of a skin rash or itching
- Any yellowing of your skin or the whites of your eyes
- Epileptic fits or convulsions

There have been reports of blood disorders which may be characterised by fever or chills, sore throat, ulcers in your mouth or throat, unusual tiredness or weakness, unusual bleeding or unexplained bruises.

Part of the intestine may become paralysed and this may lead to constipation, a swollen stomach, fever and vomiting.

Tell your doctor immediately if you notice any of these symptoms.

The following side effects are often mild and may wear off after a few days' treatment. If they are severe or last more than a few days, tell your doctor.

- Dry mouth, blurred vision, constipation or difficulty in passing water
- Fatigue, dizziness, drowsiness, headache or confusion
- Nausea, vomiting and diarrhoea
- Shakiness or the hands, increased perspiration or hot flushes
- Increased appetite/weight gain

Other side effects which may occur include hallucinations, excitement, feeling anxious, restlessness, sleeping problems, nightmares, numbness or pins and needles, a ringing in the ears, speech impairment, abnormal muscle movements or twitching, unsteadiness, coma, eye problems, dilated pupils, abdominal pain, sensitivity to light, swollen face or tongue, loss of appetite, weight loss, sore mouth, black tongue, unpleasant taste, swollen testicles, breast swelling, impotence and other sexual problems, secretion of milk from the breasts, high or low blood sugar, having to pass water frequently and hair loss. High doses or overdosage may lead to heart problems. Mood changes after stopping treatment have been reported rarely.

If your child is being treated with amitriptyline for night bedwetting you may notice a change in his/her behaviour.

If you develop any unusual symptoms or you are concerned about anything or you experience any other unwanted effects, consult your doctor.

How should you store this medicine?

Do not store above 25°C. Store in the original container. Keep the container tightly

closed. Keep out of the reach and sight of children.

Do not use the tablets after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Remember: This medicine has been prescribed for you. Do not give it to anybody else even if their symptoms appear to be the same as yours, since it may be harmful to them.

Last revision date: December 2005

LABELLING

Amitriptyline 25 mg tablets

Each tablet contains 25 mg amitriptyline hydrochloride

Also contains lactose, sucrose and E110

For oral use.

Please read the enclosed leaflet carefully before taking this medicine

Use as directed by a physician

Swallow the tablets with water

Do not store above 25°C

Store in the original container

Keep the container tightly closed

Keep all medicines out of the reach of children

50/100/250/500 tablets

MA holder: OBG Pharmaceuticals Ltd

Reeds Lane

Moreton

Wirrel CH46 1DW

PL 15755/0028

BN

Exp

POM