Public Assessment Report

Decentralised Procedure

Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution

Amitriptyline hydrochloride

UK/H/2624/001-2/DC
UK licence no: PL 29831/0356 & 0439

Wockhardt UK Limited
Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution

LAY SUMMARY

On 14th July 2010, Cyprus, Ireland, Malta, Poland and the UK agreed to grant marketing authorisations to Wockhardt UK Limited for the medicinal products Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution. The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 27th August 2010.

Amitriptyline belongs to a group of medicines known as tricyclic antidepressants. Everybody has substances called serotonin and noradrenaline in their brains. It is thought that people with depression (and some other conditions) have less of these substances compared to those without depression (or other conditions). Amitriptyline works by increasing the amounts of these substances in the brain. Amitriptyline also affects the muscles in the bladder and reduces the need to pass urine.

Amitriptyline Oral Solution is a prescription-only medicine (POM) used in the treatment of depression (especially when associated with sleep disturbance) and night-time bed-wetting.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
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<td><strong>Active Substance</strong></td>
<td>Amitriptyline hydrochloride</td>
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<tr>
<td><strong>Form</strong></td>
<td>Oral Solution</td>
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<tr>
<td><strong>Strength</strong></td>
<td>25mg/5ml and 50mg/5ml</td>
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</table>
| **MA Holder** | Wockhardt UK Limited  
Ash Road North Wrexham Industrial Estate  
Wrexham  
LL13 9UF  
United Kingdom |
| **RMS** | UK |
| **CMSs** | Cyprus, Ireland, Malta and Poland |
| **Procedure Number** | UK/H/2624/001-2/DC |
| **Timetable** | Day 210 – 14th July 2010 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Amitriptyline Hydrochloride 25mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml of solution contains 25mg amitriptyline hydrochloride.

Excipients
Each 5ml of solution contains:
1mg propyl hydroxybenzoate (E216)
6mg methyl hydroxybenzoate (E218)
3.35g liquid maltitol
Approximately 10.5mg ethanol
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral solution.
A clear pale yellow solution with an orange/tangerine odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Amitriptyline is indicated for the treatment of:
- Symptoms of depression (especially where sedation is required).
- Nocturnal enuresis where organic pathology is excluded.

4.2 Posology and method of administration
For oral administration only
Therapy should be started with a low dosage and increased gradually, according to the clinical response and any evidence of intolerance.
Adults - initial dosage: Usually 75mg a day in divided doses (or a single dose at night). If necessary, this may be increased to a total of 150mg a day, the additional doses being given in the late afternoon and/or at bedtime. The sedative effect is usually rapidly apparent. The antidepressant activity may be seen within three or four days or may take up to 30 days to develop adequately.
Adults - maintenance dosage: Usually 50 - 100mg a day. For maintenance therapy, the total dosage may be given in a single dose preferably in the evening or at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. Maintenance therapy should be continued for three months or longer to lessen the chances of relapse.
Children: Due to lack of clinical experience amitriptyline is not recommended for the treatment of depression in children under 16 years of age.
Enuresis: Children aged 6 - 10 years may receive 10 - 20mg a day, while those aged 11 - 16 may need 25 - 50mg a day. 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, porphyria, lactation, children under 6 years of age. See also sections 4.4 and 4.6.

4.4 Special warnings and precautions for use
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.
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.
Elderly patients are particularly liable to experience adverse reactions especially agitation, confusion and postural hypotension.
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.

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

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

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).

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.

Other psychiatric conditions for which amitriptyline is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be comorbid 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.

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.

Excipient Warnings

This product contains liquid maltitol. Patients with rare hereditary problems of fructose should not take this medicine. Daily quantities of 10g or more may have a mild laxative effect. Calorific value 2.3 kcal/g maltitol.

Methyl and propyl hydroxybenzoates are contained in this product which may cause allergic reactions (possibly delayed).

This product contains small amounts of ethanol (alcohol), less than 100mg per dose.

4.5 Interaction with other medicinal products and other forms of interaction

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 a MAOI and starting amitriptyline which should be introduced cautiously and dosage increased gradually. 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.

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

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

Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with drugs having an anticholinergic action.
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. Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants. Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients treated with 1g ethchlorvynol and 75mg to 150mg amitriptyline. St John's Wort may decrease plasma levels of amitriptyline. Amitriptyline may increase levels of thioridazine leading to cardiac side effects.

4.6 Pregnancy and lactation

The safety of amitriptyline for use during pregnancy has not been established. Amitriptyline is not recommended during pregnancy, especially during the first and third trimesters unless there are compelling reasons, and in these patients the benefits should be weighed against the possible hazards to the foetus, child or mother. Clinical experience of the use of amitriptyline in pregnancy has been limited. Animal studies have shown harmful effects at exceptionally high doses. Breast feeding mothers: Amitriptyline is detectable in breast milk. Because of the potential for 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 impair alertness in some patients and activities made hazardous by diminished alertness (e.g. driving a car) should be avoided.

4.8 Undesirable effects

In general, amitriptyline is well tolerated. The side effects given below are essentially a combined list of all those of the tricyclic group of antidepressants. Some of them have not been reported with amitriptyline, but are included because of the similar pharmacologies of the group members. As the antidepressant effects of amitriptyline may not become apparent for the first 2-4 weeks of therapy, patients should be closely monitored during this period.

Blood and lymphatic system disorders: Bone marrow depression including agranulocytosis, leucopenia, eosinophilia, purpura, thrombocytopenia.

Immune system disorders: Skin rash, urticaria, photosensitisation, oedema of face and tongue.

Endocrine disorders: Testicular swelling, gynaecomastia, breast enlargement, galactorrhoea, increased or decreased libido, impotence, interference with sexual function, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Metabolism and nutrition disorders: Elevation or lowering of blood sugar levels, weight loss, increased appetite and weight gain (may be a drug reaction or due to relief of the depression).

Nervous system disorders: Dizziness, weakness, drowsiness, fatigue, headache, confusional states, disturbed concentration, disorientation, delusions, hallucinations, hypomania, excitement, anxiety, restlessness, insomnia, nightmares, numbness, tingling and paraesthesia of the extremities, peripheral neuropathy, inco-ordination, ataxia, tremors, coma, convulsions, alteration of the ECG, extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria, tinnitus. Cases of suicidal ideation and suicidal behaviours have been reported during amitriptyline therapy or early after treatment discontinuation (see section 4.4). Anticholinergic effects include: dry mouth, blurred vision, disturbance of accommodation, increased intra-ocular pressure, constipation, paralytic ileus, hyperpyrexia, urinary retention, urinary tract dilatation.

Eye disorders: mydriasis.

Cardiovascular disorders: 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.

Gastro-intestinal disorders: Nausea, epigastric distress, vomiting, anorexia, stomatitis, unpleasant taste, diarrhoea, parotid swelling, black tongue.

Hepato-biliary disorders: Rarely hepatitis (including altered liver function and jaundice).

Skin and subcutaneous tissue disorders: Increased perspiration, alopecia.

Renal and urinary disorders: Urinary frequency.

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 or dosage reduction. These symptoms are not indicative of addictions.
Adverse reactions such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants 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.

4.9 **Overdose**
Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic drugs.
Overdose effects are mainly due to anticholinergic (atropine-like) effects at autonomic nerve endings and in the brain. There is also a quinidine-like effect on the myocardium.
**Peripheral symptoms**
Commonly include sinus tachycardia, hot dry skin, dry mouth and tongue, dilated pupils and urinary retention.
The most important ECG feature of toxicity is prolongation of the QRS interval, which indicates a high risk of ventricular tachycardia. In very severe poisoning the ECG may be bizarre. Rarely, prolongation of the PR interval or heart block may occur. QT interval prolongation and torsade de pointes has also been reported.
**Central symptoms**
Commonly include ataxia, nystagmus and drowsiness, which may lead to deep coma and respiratory depression. Increased tone and hyperreflexia may be present with extensor plantar reflexes. In deep coma all reflexes may be abolished. A divergent squint may be present.
Hypotension and hypothermia may occur. Fits occur in >5% of cases.
During recovery confusion, agitation and visual hallucinations may occur.
**Management**
An ECG should be taken and in particular the QRS interval should be assessed since prolongation signifies an increased risk of arrhythmia and convulsions. Give activated charcoal by mouth or nasogastric tube if more than 4 mg/kg has been ingested within one hour, provided the airway can be protected. A second dose of charcoal should be considered after two hours in patients with central features of toxicity who are able to swallow.
Tachyarrhythmias are best treated by correction of hypoxia and acidosis. Even in the absence of acidosis 50 millimoles of sodium bicarbonate should be given by intravenous infusion to adults with arrhythmias or clinically significant QRS prolongation on the ECG.
Control convulsions with intravenous diazepam or lorazepam. Give oxygen and correct acid base and metabolic disturbances. Phenytoin is contraindicated in tricyclic overdosage, because, like tricyclic antidepressants, it blocks sodium channels and may increase the risk of cardiac arrhythmias. Glucagon has been used to correct myocardial depression and hypotension.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
ATC Code: N06A A
Amitriptyline is a tricyclic antidepressant which mode of action in depression is not fully understood. It has anticholinergic and sedative properties.
It prevents the re-uptake of noradrenaline and serotonin at nerve terminals.

5.2 **Pharmacokinetic properties**
Amitriptyline is readily absorbed from the gastro intestinal tract. Peak plasma concentrations occur within about 6 hours of oral administration. Since amitriptyline slows gastro intestinal transit time, absorption may be delayed, particularly in overdosage. Amitriptyline is demethylated in the liver to the primary active metabolite, nortriptyline. The metabolism pathway includes N-oxidation and conjugation with glucuronic acid. It is distributed extensively into plasma and tissue protein. It has a half life from 9 to 25 hours. It will cross the placental barrier and is excreted in breast milk. It is excreted in urine in the form of metabolites.

5.3 **Preclinical safety data**
None known
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Methyl hydroxybenzoate (E218)
Propyl hydroxybenzoate (E216)
Propylene glycol
Ascorbic acid
Quinoline yellow (E104)
Orange flavour 10950-56 (contains ethanol).
Orange/tangerine flavour 10888-56 (contains ethanol).
Sucralose powder
Liquid maltitol
Purified water.

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
Unopened: 24 months
After first opening: 1 month

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original bottle and outer carton in order to protect from light.

6.5 Nature and contents of container
150 ml amber soda glass (type III) bottle fitted with a 28 mm white child resistant tamper evident cap, with expanded polyethylene (EPE) liner, and outer cardboard carton.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0356

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/08/2010

10 DATE OF REVISION OF THE TEXT
27/08/2010
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   Approximately 10.5mg ethanol

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- Symptoms of depression (especially where sedation is required).
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Adults - initial dosage: Usually 75mg a day in divided doses (or a single dose at night). If necessary, this may be increased to a total of 150mg a day, the additional doses being given in the late afternoon and/or at bedtime. The sedative effect is usually rapidly apparent. The antidepressant activity may be seen within three or four days or may take up to 30 days to develop adequately.
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4.6 Pregnancy and lactation
The safety of amitriptyline for use during pregnancy has not been established. Amitriptyline is not recommended during pregnancy, especially during the first and third trimesters unless there are compelling reasons, and in these patients the benefits should be weighed against the possible hazards to the foetus, child or mother. Clinical experience of the use of amitriptyline in pregnancy has been limited. Animal studies have shown harmful effects at exceptionally high doses. Breast feeding mothers: Amitriptyline is detectable in breast milk. Because of the potential for serious adverse reactions in infants from amitriptyline, a decision should be made whether to discontinue breast feeding or discontinue the drug.

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

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In general, amitriptyline is well tolerated. The side effects given below are essentially a combined list of all those of the tricyclic group of antidepressants. Some of them have not been reported with amitriptyline, but are included because of the similar pharmacologies of the group members. As the antidepressant effects of amitriptyline may not become apparent for the first 2-4 weeks of therapy, patients should be closely monitored during this period.

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Endocrine disorders: Testicular swelling, gynaecomastia, breast enlargement, galactorrhoea, increased or decreased libido, impotence, interference with sexual function, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Metabolism and nutrition disorders: Elevation or lowering of blood sugar levels, weight loss, increased appetite and weight gain (may be a drug reaction or due to relief of the depression).

Nervous system disorders: Dizziness, weakness, drowsiness, fatigue, headache, confusional states, disturbed concentration, disorientation, delusions, hallucinations, hypomania, excitement, anxiety, restlessness, insomnia, nightmares, numbness, tingling and paraesthesia of the extremities, peripheral neuropathy, inco-ordination, ataxia, tremors, coma, convulsions, alteration of the ECG, extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria, tinnitus.

Cases of suicidal ideation and suicidal behaviours have been reported during amitriptyline therapy or early after treatment discontinuation (see section 4.4). Anticholinergic effects include: dry mouth, blurred vision, disturbance of accommodation, increased intra-ocular pressure, constipation, paralytic ileus, hyperpyrexia, urinary retention, urinary tract dilatation.

Eye disorders: mydriasis.

Cardiovascular disorders: 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.

Gastro-intestinal disorders: Nausea, epigastric distress, vomiting, anorexia, stomatitis, unpleasant taste, diarrhoea, parotid swelling, black tongue.

Hepato-biliary disorders: Rarely hepatitis (including altered liver function and jaundice). Skin and subcutaneous tissue disorders: Increased perspiration, alopecia.

Renal and urinary disorders: Urinary frequency.

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 or dosage reduction. These symptoms are not indicative of addictions.

Adverse reactions such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants 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.

4.9 Overdose
Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic drugs.

Overdose effects are mainly due to anticholinergic (atropine-like) effects at autonomic nerve endings and in the brain. There is also a quinidine-like effect on the myocardium.

Peripheral symptoms
Commonly include sinus tachycardia, hot dry skin, dry mouth and tongue, dilated pupils and urinary retention.
The most important ECG feature of toxicity is prolongation of the QRS interval, which indicates a high risk of ventricular tachycardia. In very severe poisoning the ECG may be bizarre. Rarely, prolongation of the PR interval or heart block may occur. QT interval prolongation and torsade de pointes has also been reported.

Central symptoms
Commonly include ataxia, nystagmus and drowsiness, which may lead to deep coma and respiratory depression. Increased tone and hyperreflexia may be present with extensor plantar reflexes. In deep coma all reflexes may be abolished. A divergent squint may be present.

Hypotension and hypothermia may occur. Fits occur in >5% of cases.
During recovery confusion, agitation and visual hallucinations may occur.

Management
An ECG should be taken and in particular the QRS interval should be assessed since prolongation signifies an increased risk of arrhythmia and convulsions. Give activated charcoal by mouth or nasogastric tube if more than 4 mg/kg has been ingested within one hour, provided the airway can be protected. A second dose of charcoal should be considered after two hours in patients with central features of toxicity who are able to swallow.

Tachyarrhythmias are best treated by correction of hypoxia and acidosis. Even in the absence of acidosis 50 millimoles of sodium bicarbonate should be given by intravenous infusion to adults with arrhythmias or clinically significant QRS prolongation on the ECG.

Control convulsions with intravenous diazepam or lorazepam. Give oxygen and correct acid base and metabolic disturbances. Phenytoin is contraindicated in tricyclic overdosage, because, like tricyclic antidepressants, it blocks sodium channels and may increase the risk of cardiac arrhythmias. Glucagon has been used to correct myocardial depression and hypotension.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC Code: N06A A

Amitriptyline is a tricyclic antidepressant which mode of action in depression is not fully understood. It has anticholinergic and sedative properties.
It prevents the re-uptake of noradrenaline and serotonin at nerve terminals.

5.2 Pharmacokinetic properties
Amitriptyline is readily absorbed from the gastro intestinal tract. Peak plasma concentrations occur within about 6 hours of oral administration. Since amitriptyline slows gastro intestinal transit time, absorption may be delayed, particularly in overdosage. Amitriptyline is demethylated in the liver to the primary active metabolite, nortriptyline. The metabolism pathway includes N-oxidation and conjugation with glucuronic acid. It is distributed extensively into plasma and tissue protein. It has a half life from 9 to 25 hours. It will cross the placental barrier and is excreted in breast milk. It is excreted in urine in the form of metabolites.

5.3 Preclinical safety data
None known
6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Methyl hydroxybenzoate (E218)
Propyl hydroxybenzoate (E216)
Propylene glycol
Ascorbic acid
Quinoline yellow (E104)
Orange flavour 10950-56 (contains ethanol).
Orange/tangerine flavour 10888-56 (contains ethanol).
Sucralose powder
Liquid maltitol
Purified water.

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
Unopened: 24 months
After first opening: 1 month

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original bottle and outer carton in order to protect from light.

6.5 Nature and contents of container
150 ml amber soda glass (type III) bottle fitted with a 28 mm white child resistant tamper evident cap, with expanded polyethylene (EPE) liner, and outer cardboard carton.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0439

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/08/2010

10 DATE OF REVISION OF THE TEXT
27/08/2010
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Amitriptyline Hydrochloride 25mg/5ml oral solution
Amitriptyline Hydrochloride 50mg/5ml oral solution

Read all of this leaflet carefully before you start to take this medicine.
- Keep this leaflet. You may need to read it again while you are receiving your treatment.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Amitriptyline Oral Solution is and what it is used for
2. Before you take Amitriptyline Oral Solution
3. How to take Amitriptyline Oral Solution
4. Possible side effects
5. How to store Amitriptyline Oral Solution
6. Further information

1. What Amitriptyline Oral Solution is and what it is used for

The name of your medicine is Amitriptyline Oral Solution. Amitriptyline belongs to a group of medicines known as tricyclic antidepressants. Everybody has substances called serotonin and noradrenaline in their brains. It is thought that people with depression (and some other conditions) have less of these substances compared to those without depression (or other conditions). Amitriptyline works by increasing the amounts of these substances in the brain. Amitriptyline also affects the muscles in the bladder and reduces the need to pass urine.

Amitriptyline Oral Solution is used in the treatment of:
- depression (especially when associated with sleep disturbance)
- night-time bed-wetting.

2. Before you take Amitriptyline Oral Solution
You should not take Amitriptyline Oral Solution if you:
- are allergic (hypersensitive) to amitriptyline or to any of the other ingredients in Amitriptyline Oral Solution (see section 4. Further information)
- are taking drugs called Monoamine Oxidase Inhibitors (MAOIs) for depression
- are recovering from a heart attack
- have an abnormal heart rhythm
- suffer from mania (feeling high or over-excitement)
- have severe liver disease
- suffer from porphyria (a disease of blood proteins affecting the skin, gut and nervous system)
- are breast feeding.

Amitriptyline Oral Solution should not be used in children under 6 years.

Amitriptyline Oral Solution is not recommended for the treatment of depression in children under 18 years of age.

Talk to your doctor before taking Amitriptyline Oral Solution if you:
- suffer from epilepsy
- suffer from liver disease
- have problems passing water
- have an enlarged prostate
- have increased pressure in your eyes (e.g. glaucoma)
- suffer from heart disease
- have an overactive thyroid gland
- are taking medicines for thyroid disease
- suffer from schizophrenia
- receive electroconvulsive therapy (ECT)
- are due to have surgery in the near future.

Special care should be taken with elderly patients.

Thoughts of suicide and worsening of your depression or anxiety disorder
If you are depressed you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines take time to work, usually about two weeks but sometimes longer. You may be more likely to have these kinds of thoughts if:
- you have previously had thoughts about killing yourself
- you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts about harming or killing yourself at any time, contact your doctor or go to hospital straight away. You may find it helpful to talk to a close friend or relative that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is important you do this as some medicines when taken in combination with Amitriptyline Oral Solution can
cause a very serious side effect called paralytic ileus (this is when the small bowel ceases to function for a time). The following medicines can affect or be affected by treatment with Amitriptyline Oral Solution:

- antidepressants called monoamine oxidase inhibitors (MAOIs) — you should wait at least 14 days after stopping an MAOI before starting Amitriptyline
- medicines used to treat high blood pressure (e.g. quinapril, debrisoquin, bethanidine, cotidine)
- medicines used as sedatives to treat sleep problems (e.g. etizolam, zolpidem)
- medicines used to maintain blood pressure in critically ill patients (e.g. ephedrine, isoprenaline, noradrenaline, phenoxybenzamine)
- disulfram (used to treat alcoholism)
- ritonavir (used to treat HIV infection)
- cimetidine (used to treat problems with stomach acid)
- thiadiazine (used to treat schizophrenia and psychosis)
- St John’s Wort (a herbal remedy often used for depression)

Taking Amitriptyline Oral Solution with food and drink
As with all medicines that act on the central nervous system, it is advised that you do not drink alcohol while taking this medicine.

Pregnancy and breast-feeding
You should not use this medicine if you are pregnant unless your doctor specifically recommends it. Tell your doctor straight away if you think you may be pregnant or wish to become pregnant.

You should not take Amitriptyline Oral Solution if you are breast feeding.

Driving and using machinery
Amitriptyline oral solution may cause drowsiness and reduced alertness, do not drive or operate machinery while taking this medicine.

Important information about some of the ingredients in Amitriptyline Oral Solution
This medicine contains:
- Matteol: if you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicine.
- small amounts of ethanol (alcohol), less than 100mg per dose.
- preservatives known as par hydroxybenzoates; these ingredients may cause allergic reactions and could happen some time after starting the medicine.

3. How to take Amitriptyline Oral Solution
Always take Amitriptyline Oral Solution as your doctor has told you. Your doctor will decide the right dose for you; this will be on the pharmacist's label. Check this carefully, it will tell you how much of this medicine to take and how often to take it. This medicine should be swallowed. The usual dose are as follows:

Adults
- usual starting dose is 75mg given twice or as one dose before bedtime
- this may be increased to 150mg a day, given as one dose in the evening or before bedtime
- when an improvement is seen in your condition, your doctor will reduce the dose.

Children (Eurosia)
- children aged 6-10 years may receive 10-20mg a day
- children aged 11-16 years may need 25-50mg a day
- treatment should be no longer than 3 months.

4. If you take too much Amitriptyline Oral Solution then you should
If you (or anybody else, including a child), takes more Amitriptyline Oral Solution than you should you should contact your doctor or nearest hospital casualty department immediately. Always take the bottle and leaflet with you.

If you forget to take Amitriptyline Oral Solution
If you forget a dose, take another as soon as you remember. If it is almost time for your next dose, then do not take the missed dose at all. NEVER take a double dose to make up for the one missed.

If you stop taking Amitriptyline Oral Solution
Do not stop taking Amitriptyline Oral Solution unless you have been told to do so by your doctor. If you suddenly stop your treatment you may experience side effects such as nausea, headache and general feeling of unwell.

Even with gradual withdrawal of treatment you may still experience some side effects in the first two weeks such as irritability, restlessness and dream and sleep disturbances. Rarely, some patients develop mania (persistent extremely elevated mood and sometimes psychosis) and hypomania (mild form of mania) within 2-7 days of stopping long-term therapy of Amitriptyline.

4. Possible side effects
Like all medicines, Amitriptyline Oral Solution can cause side effects, although not everybody gets them. As can happen with any medicine, a few people may develop an allergic reaction. If you experience any of the following, seek medical help immediately:
- rash, itching, difficulty breathing.

Side effects that have been reported with Amitriptyline Oral Solution are:

Heart and Blood Vessel Disorders
- high blood pressure
- fainting
- low blood pressure (particularly when standing)

Nervous System Disorders
- confusion
- disorientation
- excitement
- hearing loss
- weight gain

- heart attack
- stroke
- problems with heart rhythm
- nightmares
- reduced concentration
- hallucinations
PAR Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution

UK/H/2624/001-2/DC

- dilusions
- sleep disturbances
- involuntary movements
- fits
- headache
- problems with coordination and balance

Eye problems
- blurred vision
- enlarged pupils

Gastrointestinal System
- dry mouth
- paralysis of the gut
- stomach pains
- black tongue
- liver disease
- weight gain
- unpleasant tastes in mouth

Skin and Hair problems
- sensitivity to sunlight
- increased sweating
- hair loss
- itching
- rash

Kidney and Urinary complaints
- problems passing water
- increased urination

Muscle and Bone complaints
- painful joints
- weakness
- fatigue
- altered sex drive
- swelling of testicles
- milk production
- increase in breast tissue (in men and women)
- problems with bone marrow and blood cell production

- persistent elevated mood
- anxiety/irritability
- coma
- dizziness
- ringing in the ears
- numbness and tingling of the extremities
- problems focusing eyes
- increased pressure in the eye
- constipation
- nausea and vomiting
- altered appetite
- diarrhoea
- weight loss
- inflammation of the mouth

If you experience any side effects or feel that the medicine is affecting you badly tell your doctor or pharmacist immediately.

5. How to store Amitriptyline Oral Solution

Keep out of the reach and sight of children.
- Amitriptyline Oral Solution should not be stored above 25°C. Store in the original bottle and outer carton to protect from light; do not transfer to another container.
- Amitriptyline Oral Solution should not be taken after the expiry date on the label and carton; the expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Further information

What Amitriptyline Oral Solution contains

The active ingredient is: amitriptyline hydrochloride.

Amitriptyline Hydrochloride 25mg/5ml oral solution contains 25mg of the active ingredient in 5ml

Amitriptyline Hydrochloride 50mg/5ml oral solution contains 50mg of the active ingredient in 5ml

The other ingredients are: methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216), propylene glycol, ascorbic acid, quinoline yellow (E104), orange flavour 1060-56 (contains ethanol), orange/tangerine flavour 1088-56 (contains ethanol), saccharose powder, liquid maltitol and purified water.

What Amitriptyline Oral Solution looks like and the contents of the pack

Amitriptyline Oral Solution is a clear pale yellow solution with an orange/tangerine odour. The medicine is supplied in 150ml amber glass bottle, with a child resistant cap, in a cardboard outer carton.

Marketing Authorisation Holder: W clarkord UK Ltd, Ash Road North, Wrexham, LL13 0UF, UK.

Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 0UF, UK.

These medicinal products are authorised in the Member States of the EEA under the following names:

UK: Amitriptyline Hydrochloride 25mg/5ml oral solution and Amitriptyline Hydrochloride 50mg/5ml oral solution

Ireland: Amitriptyline Hydrochloride 25mg/5ml oral solution and Amitriptyline Hydrochloride 50mg/5ml oral solution

Cyprus: Amitriptyline Hydrochloride Wockhardt 25mg/5ml oral solution and Amitriptyline Hydrochloride Wockhardt 50mg/5ml oral solution

Malta: Amitriptyline Hydrochloride 25mg/5ml oral solution and Amitriptyline Hydrochloride 50mg/5ml oral solution

Poland: Amitriptyline Hydrochloride Wockhardt

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 199 5000 (UK Only). Please be ready to give the following information.

<table>
<thead>
<tr>
<th>Product name</th>
<th>UK Reference number</th>
<th>Irish Reference number</th>
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<tbody>
<tr>
<td>Amitriptyline 25mg/5ml Oral Solution</td>
<td>PL 29831/0429</td>
<td>PA 1339/24:2</td>
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<tr>
<td>Amitriptyline 50mg/5ml Oral Solution</td>
<td>PL 29831/0449</td>
<td>PA 1339/24:1</td>
</tr>
</tbody>
</table>

This is a service provided by the Royal National Institute of Blind People.

For the Republic of Ireland please call +353 52 36253.

The leaflet was last approved in: August 2010
Module 4
Labelling

Each 5ml of solution contains 25mg of amitriptyline hydrochloride.
Contains E216, E218, liquid maltitol and ethanol.
Read the package leaflet for further information.

Dose: As directed by your doctor

Read the package leaflet before use.
Do not store above 25°C.
Store in the original bottle and outer carton in order to protect from light.
Use within 1 month of opening.
Keep out of the reach and sight of children.

Amitriptyline Hydrochloride
25mg/5ml
Oral Solution
For oral use

150ml
PAR Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution

50mg/5ml Oral Solution

Each 5ml of solution contains 50mg of amitriptyline hydrochloride.
Contains E216, E218, liquid maize and ethanol.

Read the package leaflet for further information.

For oral use

As directed by your doctor
Read the package leaflet before use.
Do not store above 25°C.

Store in the original bottle and outer carton in order to protect from light.

Keep out of the reach and sight of children.

Marketing Authorisation holder:
Wockhardt UK Ltd, Ascot Road North, Westham, LL15 8UF, UK
PL.2905/10439 PA.1339/243/MA 154/04602

For oral use

150ml
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution, in the treatment of symptoms of depression (especially where sedation is required) and Nocturnal enuresis where organic pathology is excluded, could be approved.

These applications were submitted under Article 10(1), claiming to be generic medicinal products of Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R), which were licensed in the UK to Merck Sharp & Dohme Limited on 13th July 1983.

With UK as the RMS in these Decentralised Procedures (UK/H/2624/001-2/DC), Wockhardt UK Limited is applying for the Marketing Authorisations for Amitriptyline 25mg/5ml and 50mg/5ml Oral Solution in Cyprus, Ireland, Malta and Poland.

Amitriptyline, a dibenzocycloheptadiene, is a tricyclic antidepressant that was developed from phenothiazine compounds related to chlorpromazine and possess a 3-ring molecular structure. Amitriptyline inhibits the neuronal reuptake of noradrenaline and serotonin in the CNS. Its specific mechanism of action is not fully understood, however, prevention of the reuptake of these monoamine neurotransmitters, which potentiates their action in the brain, appears to be associated with antidepressant activity. Tricyclic antidepressants, such as amitriptyline, also possess affinity for muscarinic and histamine H1 receptors to varying degrees. Amitriptyline is one of the more sedating tricyclics.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of the originator products that have been licensed for over 10 years. No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of the originator products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant respective licences for the above products at the end of procedure (Day 210 – 14th July 2010). After a subsequent national phase, the UK granted licences for these products on 27th August 2010 (PL 29831/0356 and 0439).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the products in the Reference Member State</th>
<th>Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution</th>
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<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antidepressants (N06A)</td>
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<td>Pharmaceutical form and strength(s)</td>
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<td>Reference Member State</td>
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<tr>
<td>Concerned Member States</td>
<td>Cyprus, Ireland, Malta and Poland</td>
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<td>Marketing Authorisation Number(s)</td>
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<tr>
<td></td>
<td>Ash Road North</td>
</tr>
<tr>
<td></td>
<td>Wrexham Industrial Estate</td>
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<td></td>
<td>LL13 9UF</td>
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<td>United Kingdom</td>
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</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1  QUALITY ASPECTS

DRUG SUBSTANCE

INN:  Amitriptyline hydrochloride
Chemical Names:  3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-N,N-dimethyl-1-propanamine

Structure:

![Structure of Amitriptyline Hydrochloride](image)

Molecular formula:  $C_{20}H_{23}NHCl$
Molecular weight:  313.9
Physical form:  White to almost white crystalline powder or small crystal. Freely soluble in water, in Alcohol, and in Methylene Chloride, in Methanol and in Chloroform; insoluble in Ether.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period for active amitriptyline hydrochloride when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216), propylene glycol, ascorbic acid, quinoline yellow (E104), orange flavour 10950-56 (contains ethanol), orange/tangerine flavour 10888-56 (contains ethanol), sucralose powder, liquid maltitol, and purified water.

All excipients comply with the European Pharmacopoeia monograph with the exception of quinoline yellow (E104), orange/tangerine flavour 10888-56 (contains ethanol) and orange
flavour 10950-56 which comply with in house specification and sucralose complies with National Formulae. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The products have been developed as generic versions of the reference products Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R). The licences for Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R) were cancelled in the UK on 01/04/2008. As the reference products have been cancelled and are no longer available on the EU market, physiochemical comparisons have been made to the licensed generic medicinal products, Amitriptyline 25mg/5ml and 50mg/5ml Oral Solution (PL 00427/0115-6, Rosemont Pharmaceuticals Limited) during development and presented as supportive data.

Suitable pharmaceutical development data have been provided for these applications.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished products. Process validation has been carried out on batches of each product. The results are satisfactory.

**Finished Product Specifications**
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The finished products are supplied in amber soda glass (type III) bottle fitted with white child resistant tamper evident cap, with expanded polyethylene (EPE) liner, and outer cardboard carton. Pack size is 150ml.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set when the product is unopened and after first opening 1 month, with the storage conditions “Do not store above 25°C” and “Store in the original bottle and outer carton in order to protect from light”.

**Bioequivalence**
No bioequivalence studies are presented to support the applications and absence has been suitably justified in accordance with the “Note for guidance on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98).
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY
The pharmacological, pharmacokinetic and toxicological properties of Amitriptyline Hydrochloride are well-known.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of the environmental risk assessment.

There are no objections to the approval of these products from a pre-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

These applications are for generic medicinal products of Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R), which were licensed in the UK to Merck Sharp & Dohme Limited on 13th July 1983. The use of the reference products is well-established in the UK.

The absence of a bioequivalence study has been suitably justified in accordance with the Committee for Proprietary Medicinal Products Notes for Guideline on “Note for guidance on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98).

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.
Clinical safety
Amitriptyline hydrochloride has an acceptable adverse events profile. No new safety data are supplied or required for these generic applications. Amitriptyline hydrochloride has a well-established side-effect profile and is generally well-tolerated.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms
The MAA forms are medically satisfactory.

Clinical Conclusion
There are no objections to the approval of these products from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
The pre-clinical data submitted have not revealed any evidence of potential risks to human health from treatment with Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution beyond those already described.

EFFICACY
These applications are for generic medicinal products of Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R), which were licensed in the UK to Merck Sharp & Dohme Limited on 13th July 1983. The use of the reference products is well-established in the UK.

The proposed products were considered to contain the same quantitative and qualitative composition of the active substance as their respective reference products and the absence of a bioequivalence study has been suitably justified in accordance with the Committee for Proprietary Medicinal Products “Note for guidance on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98).

No new safety data are supplied or required for these generic applications. Amitriptyline hydrochloride has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with amitriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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