Amtriptyline Hydrochloride 10mg/5ml Oral Solution

PL 29831/0460

UKPAR

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AMITRIPTYLINE HYDROCHLORIDE 10MG/5ML ORAL SOLUTION

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LAY SUMMARY

This is a summary of the public assessment report (PAR) for Amitriptyline Hydrochloride 10mg/5ml Oral Solution (PL 29831/0460). It explains how Amitriptyline Hydrochloride 10mg/5ml Oral Solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Amitriptyline Hydrochloride 10mg/5ml Oral Solution.

For practical information about using Amitriptyline Hydrochloride 10mg/5ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Amitriptyline Hydrochloride 10mg/5ml Oral Solution and what is it used for?
Amitriptyline Hydrochloride 10mg/5ml Oral Solution is a ‘generic medicine’. This means that it is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Tryptizol 10mg Tablets.

Amitriptyline Hydrochloride 10mg/5ml Oral Solution belongs to a group of medicines known as tricyclic antidepressants. It is used in the treatment of depression (especially when associated with sleep disturbance) and night-time bed-wetting.

How does Amitriptyline Hydrochloride 10mg/5ml Oral Solution work?
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.

How is Amitriptyline Hydrochloride 10mg/5ml Oral Solution used?
When Amitriptyline Hydrochloride 10mg/5ml Oral Solution is used to treat depression in adults the 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 in the patient’s condition is seen the doctor will reduce the dose.

When Amitriptyline Hydrochloride 10mg/5ml Oral Solution is used to treat bed-wetting (enuresis) in children aged 6-10 years they may receive 10-20mg a day. Children aged 11-16 years may need 25-50mg a day. Treatment of bed-wetting in children should be no longer than 3 months.

The medicine can only be obtained with a prescription.
What benefits of Amitriptyline Hydrochloride 10mg/5ml Oral Solution have been shown in studies?
Information about how amitriptyline hydrochloride dissolves has been provided in the place of studies in patients to demonstrate that Amitriptyline Hydrochloride 10mg/5ml Oral Solution is bioequivalent to the reference medicine, Tryptizol 10mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body. The reasons why studies in patients were not considered necessary are discussed in more detail in the PAR.

What are the possible side effects of Amitriptyline Hydrochloride 10mg/5ml Oral Solution?
Because Amitriptyline Hydrochloride 10mg/5ml Oral Solution is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of restrictions, see the package leaflet.

Why is Amitriptyline Hydrochloride 10mg/5ml Oral Solution approved?
It was concluded that, in accordance with EU requirements, Amitriptyline Hydrochloride 10mg/5ml Oral Solution has been shown to have comparable quality and to be bioequivalent to Tryptizol 10mg Tablets. Therefore, the MHRA decided that, as for Tryptizol 10mg Tablets, the benefits of this medicine are greater than its risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Amitriptyline Hydrochloride 10mg/5ml Oral Solution?
Suitable safety information has been included in the Summary of Product Characteristics and package leaflet for Amitriptyline Hydrochloride 10mg/5ml Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Amitriptyline Hydrochloride 10mg/5ml Oral Solution
The Marketing Authorisation for Amitriptyline Hydrochloride 10mg/5ml Oral Solution was granted in the UK on 13 August 2014.

This summary was last updated in September 2014.

The full PAR for Amitriptyline Hydrochloride 10mg/5ml Oral Solution follows this summary.
AMITRIPTYLINE HYDROCHLORIDE 10MG/5ML ORAL SOLUTION

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for the medicinal product Amitriptyline Hydrochloride 10mg/5ml Oral Solution (PL 29831/0460) to Wockhardt UK Ltd on 13 August 2014. This prescription only medicine (POM) is used for the treatment of symptoms of depression (especially where sedation is required) and nocturnal enuresis where organic pathology is excluded.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal product of the reference product Tryptizol 10mg Tablets (PL 00025/0093R). Tryptizol 10mg Tablets were first authorised to Merck Sharp & Dohme Limited on 13 July 1983.

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

No non-clinical or clinical studies were conducted, which is acceptable given that reference is made to a medicinal product which has been licensed for over 10 years and the drug substance is highly soluble and permeable and there are no excipients in either the test or reference product that affect dissolution or absorption.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: AMITRIPTYLINE HYDROCHLORIDE

INN: Amitriptyline hydrochloride
Chemical names: 3-(10,11-Dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-N,N-dimethylpropan-1-amine hydrochloride
CAS: 549-18-8
Molecular formula: C20H23NHCl
Molecular weight: 313.9
Structure:

General properties: White or almost white crystalline powder or small crystals. Freely soluble in water, ethanol (96%) and in methylene chloride.

Synthesis of the drug substance from the designated starting materials 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.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised.

Appropriate specifications are provided for the drug substance, with suitable test methods and limits. Suitable certificates of analysis have been provided for all reference standards used. Batch analysis data are provided and comply with the proposed specifications.

Satisfactory specifications have been provided for all packaging used for storing the drug substance. The primary packaging has been shown to comply with current legislation concerning materials in contact with foodstuff.

Appropriate stability data have been generated showing the drug substance to be physically and chemically stable. A suitable retest period has been set based on stability data submitted for the drug substance stored in the proposed packaging.
MEDICINAL PRODUCT: AMITRIPTYLINE HYDROCHLORIDE 10MG/5ML ORAL SOLUTION

Description and composition
The product is presented as a clear, colourless to pale yellow oral solution with an orange/tangerine odour. Each 5ml of the solution contains 10mg amitriptyline hydrochloride and the excipients methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216), propylene glycol, ascorbic acid, orange flavour 10950-56 (contains ethanol), orange/tangerine flavour 10888-56 (contains ethanol), sucralose powder, liquid maltitol and purified water.

All excipients comply with their European Pharmacopoeia monographs with the exception of orange flavour 10950-56 and orange/tangerine flavour 10888-56, which are controlled in line with suitable in-house specifications and comply with Directive 2000/13/EC for flavourings. In the absence of European Pharmacopoeia monographs for these excipients this is acceptable.

None of the excipients are of animal/human origin.

Pharmaceutical Development
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the reference product, Tryptizol 10mg Tablets. The licences for Tryptizol 10mg tablets (PL 00025/0093R) were cancelled in the UK on 1 April 2008. As the reference products have been cancelled and are no longer available on the EU market, comparisons have been made to licensed generic medicinal products during development and presented as supportive data. The formulation developed was based on the licensed formulations for Amitriptyline hydrochloride 25mg/5ml and 50mg/5ml Oral Solutions (PL 29831/0356 and 0439) authorised to the applicant. A satisfactory account of the pharmaceutical development has been provided.

Manufacture
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on pilot-scale batches of finished product. The results are satisfactory. A commitment has been made to perform process validation on the first three commercial-scale batches of finished product.

Control of medicinal product
The finished product specification is satisfactory. Test methods have been described and have been 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 product is presented in 150 ml amber soda glass (type III) bottles fitted with a 28 mm white child resistant tamper evident cap, with expanded polyethylene (EPE) liner and outer cardboard carton.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

**Stability**
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 2 years for product stored in unopened bottles and of 1 month from when the bottle is first opened. This is acceptable when the storage precautions “Do not store above 25°C” and “Store in the original bottle and outer carton in order to protect from light” are applied.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solutions (PL 29831/0356 and PL 29831/0439). The bridging report submitted by the applicant has been found acceptable.

**Marketing Authorisation Application (MAA) form**
The MAA form is satisfactory from a pharmaceutical perspective.

**Quality Overall Summary**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of amitriptyline hydrochloride are well-known, no non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No new pharmacokinetic or pharmacodynamic data were submitted with this application. The product does not meet the criteria for a Biopharmaceutics Classification System (BCS) biowaiver as it is a different dose form, however the lack of data was deemed acceptable as amitriptyline hydrochloride is a BCS Class I drug (high solubility and complete absorption), and there are no excipients in either the test or reference products that affect dissolution or absorption.

Efficacy
No new data on efficacy have been submitted and none are required for this type of application.

SAFETY
No new data on safety have been submitted and none are required for this type of application.

EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
This is consistent with the SmPC for the reference product and is satisfactory.

PATIENT INFORMATION LEAFLETS (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
This is satisfactory

MARKETING AUTHORISATION APPLICATION (MAA) FORM
The MAA form is satisfactory from a clinical perspective.

CONCLUSION
The grant of a Marketing Authorisation is recommended for this application.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Amitriptyline Hydrochloride 10mg/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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for this type of application.

CLINICAL
No bioequivalence studies were conducted.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amitriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
AMITRIPTYLINE HYDROCHLORIDE 10MG/5ML ORAL SOLUTION

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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 24 May 2011.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 14 June 2011.
3. Following assessment of the application the MHRA requested further information relating to the dossier on 12 September 2011, 29 June 2012, 29 November 2012, 29 May 2013 and 11 October 2013.
4. The applicant responded to the MHRA’s requests, providing further information on 6 February 2012, 1 October 2012, 4 March 2013, 2 September 2013 and 2 December 2013.
5. The application was granted on 13 August 2014.
STEPS TAKEN AFTER INITIAL AUTHORISATION – SUMMARY

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Label:

Amitriptyline Hydrochloride

10mg/5ml Oral Solution
(sugar free)

For oral use

Each 5ml of solution contains 10mg 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 sight and reach of children.

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Marketing Authorisation Holder:
Woodwards UK Ltd.
Ash Road North,
Wrexham, LL13 9UF, UK
105401/1
Carton:

Each 15ml of solution contains 10mg of amitriptyline hydrochloride.
Contains E211, E133, liquid maltitol and ethanol. Read the package leaflet for further information.

Store: As directed by your doctor.

Read the package leaflet before use.

Do not store above 30°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 sight and reach of children.

Marketing Authorisation Holder: Warwickshire UK Ltd, Ash Road North,
Winnaham, LL13 0UX, UK.

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10mg/5ml Oral Solution (sugar free)