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Public Assessment Report

Name of the Product:

Lordestin

0.5 mg/ml oral solution

(desloratadine)

Procedure number: HU/H/0313/002/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 28 April 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Lordestin 0.5 mg/ml oral solution. The holder of the marketing authorisation is Gedeon Richter Plc.

The active substance is desloratadine (as desloratadine hemisulphate).

The other ingredients are propylene glycol (E1520), sorbitol, liquid (non-crystallising) (E420), citric acid, anhydrous (E330), sodium citrate (E331), sodium cyclamate (E952), hypromellose (type 2910), disodium edetate, almond flavour (propylene glycol, heliotropine, benzaldehyde, vanillin, acetophenone, anisyl alcohol, anisaldehyde, dihydrocoumarin) and purified water.

Clear, colourless almond flavoured oral solution, its pH = 3.0-3.8, packed into amber glass bottles. Each bottle is closed with a child-proof screw cap white PP 28. All packages are supplied with dyed white polystyrene (PS) double measuring spoon for doses of 2.5 ml and 5 ml. The bottles are packed into a cardboard carton with a leaflet enclosed in each box.

The active substance desloratadine is an antihistamine.

Lordestin oral solution is an antiallergy medicine that does not make the patient drowsy. It helps control the allergic reaction and its symptoms.

Lordestin oral solution relieves symptoms associated with allergic rhinitis (inflammation of the nasal passages caused by an allergy, for example, hay fever or allergy to dust mites) in adults, adolescents and children 1 year of age and older. These symptoms include sneezing, runny or itchy nose, itchy palate, and itchy, red or watery eyes.

Lordestin oral solution is also used to relieve the symptoms associated with urticaria (a skin condition caused by an allergy). These symptoms include itching and hives.

Relief of these symptoms lasts a full day and helps you to resume your normal daily activities and sleep.

What patients need to know before taking Lordestin oral solution

Those, who are allergic to desloratadine, or to any of the other ingredients of this medicine, *should not take Lordestin oral solution*.

Warnings and precautions

Those who have poor kidney function should take special care with Lordestin oral solution

Children and adolescents: this medicine should not be given to children less than 1 year of age.

Other medicines and Lordestin oral solution

There are no known interactions of Lordestin oral solution with other medicines.

Lordestin oral solution with food and drink

Lordestin oral solution may be taken with or without a meal.

Pregnancy, breast-feeding and fertility

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask theirr doctor for advice before taking this medicine. Taking Lordestin oral solution is not recommended if during pregnancy or nursing a baby.

There is no data available on male/female fertility.

Driving and using machines

At the recommended dose, this medicine is not expected to affect the ability to drive or use machines. Although most people do not experience drowsiness, it is recommended not to engage in activities requiring mental alertness, such as driving a car or operating machinery until the patient has established his/her own response to this medicinal product.

Lordestin oral solutioncontains sorbitol

Those who have been told by their doctor that they have an intolerance to some sugars, contact their doctor before taking this medicinal product.

How to take Lordestin oral solution

For children 1 through 5 years of age the recommended dose is 2.5 ml of oral solution once a day.

For children 6 through 11 years of age the recommended dose is 5 ml of oral solution once a day.

From 12 years of age and over the recommended dose is 10 ml of oral solution once a day.

Lordestin oral solution is provided with a double-ended dosing spoon suitable to measure 2.5 ml and 5 ml volumes. It should be used to take the appropriate amount of oral solution. 10 ml doses can be measured by taking two spoons of oral solution with the larger (5 ml) end.

After swallowing the dose of oral solution some water should be consumed. This medicine may be taken with or without food.

Regarding the duration of treatment, the physician will determine the type of allergic rhinitis the patient is suffering from and will determine for how long Lordestin oral solution should be taken.

If the allergic rhinitis is intermittent (presence of symptoms for less than 4 days per week or for less than 4 weeks), the physician will recommend a treatment schedule that will depend on the evaluation of the history of your disease.

If the allergic rhinitis is persistent (presence of symptoms for 4 days or more per week and for more than 4 weeks), the physician may recommend a longer term treatment.

For urticaria, the duration of treatment may be variable from patient to patient and therefore the instructions of the physician should be followed.

What happens if more Lordestin oral solution was taken than prescribed

Although Lordestin oral solution should only be taken as it is prescribed, no serious problems are expected with accidental overdose. However, more Lordestin oral solution is taken than it was told to, the doctor should be contacted immediately.

What to do if taking Lordestin oral solution was forgotten

If taking a dose on time was forgotten, it should be taken as soon as possible and then go back to the regular dosing schedule. Double dose should not be taken to make up for a forgotten dose.

Possible side effects

Like all medicines, Lordestin oral solution can cause side effects, although not everybody experiences them.

In most children and adults, side effects with desloratadine were about the same as with a dummy solution or tablet. However, common side effects in children less than 2 years of age were diarrhoea, fever and insomnia while in adults, fatigue, dry mouth and headache were reported more often than with a dummy tablet.

During the marketing of desloratadine, cases of severe allergic reactions (difficulty in breathing, wheezing, itching, hives and swelling) and rash have been reported very rarely.

Moreover, the following side effects were reported as very rare (that may affect up to 1 in 10,000 people:

- rash

- pounding or irregular heartbeat
- fast heartbeat
- stomach ache
- feeling sick (nausea)
- vomiting
- upset stomach
- diarrhoea
- dizziness
- drowsiness
- inability to sleep
- muscle pain
- hallucinations
- seizures
- restlessness with increased body movement
- liver inflammation
- abnormal liver function tests

How to store Lordestin oral solution

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

To be used in maximum 4 weeks after the first opening of the bottle.

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Lordestin 0.5 mg/ml oral solution. The procedure was finalised at 9 March 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Latvia, Poland and Romania) concerned the generic version of an oral solution of desloratadine.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application) and therefore contained no new non-clinical or clinical data, other than supporting literature where necessary. The originator product to which bioequivalence was claimed was Aerius 0.5 mg/ml oral solution (Schering-Plough, Europe), authorised for marketing since 2001 in the European Union.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Lordestin 0.5 mg/ml oral solution. The holder of the marketing authorisation is Gedeon Richter Plc, Hungary.

The product is indicated for in adults, adolescents and children over the age of 1 year for the relief of symptoms associated with allergic rhinitis and urticaria.

The maximum daily dose recommended is 5 mg from 12 years of age and over; 1.25mg in children 1 through 5 years of age and 2.5mg in children 6 through 11 years of age.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the decentralized application of Lordestin 0.5 mg/ml oral solution based on article 10(1) of Directive 2001/83/EC (generic application).

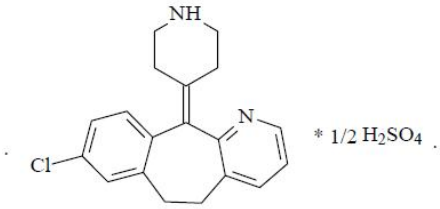
The product has been developed by Gedeon Richter Plc. The reference product Aerius 0.5 mg/ml oral solution was authorized in the EU for Merck Sharp & Dohme Ltd. *via* centralized procedure.

The drug product is indicated for the relief of symptoms associated with allergic rhinitis and urticaria.

II.2 Drug substance

Data on the quality and manufacture of the desloratadine active substance (in the form of hemisulfate salt) were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure. The Quality Overall Summary is adequate.

INN name: desloratadine
Chemical name: 5H-Benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene) hemisulphate
Structure:



The active substance is a white to almost white crystalline powder which is freely soluble in water. According to the literature and the manufacturer's experience polymorphism of desloratadine hemisulphate does not occur.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by IR, ^{1}H-NMR spectra and mass-spectrometric examination. The impurity profile of the active substance contains information about the potential impurities including the isomer impurity as well as residual solvents.

The substance is not official in the European Pharmacopoeia (Ph. Eur.) and any other pharmacopoeias. An in-house specification has been set for desloratadine hemisulphate, which includes tests for particle size distribution, identification, assay, purity and isomer purity (HPLC), residual solvents (GC), loss on drying, heavy metals, sulphated ash, sulphate content and microbiological purity.

Testing methods not described in details in the Ph. Eur. are adequately drawn up and sufficiently validated. The reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of 30 months with the suggested storage conditions (in the original package in order to protect from light) can be granted.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of the pharmaceutical development studies was to achieve an oral solution, which presents as drug substance 0.5 mg/ml of desloratadine, and that shows essential similarity with the reference product Aerius 0.5 mg/ml oral solution, produced by Merck Sharp & Dohme Ltd.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided. The active substance in the test product is in the form of desloratadine hemisulphate whereas it is the desloratadine base in the reference product. The hemisulphate salt is freely soluble in water and the quantity of the active substance both in test and reference product is the same, 0.5 mg/ml. The amount of sorbitol which may affect the gastrointestinal transit is the same as in the reference product. The higher propylene glycol concentration of the test product is justified and accepted from the chemical-pharmaceutical point of view.

As regards impurity profile the product is shown to be similar to the reference products.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

The finished product is a clear colourless solution, with almond flavour, pH 3.0-3.8. It is marketed in three different sizes (60, 125 and 150 ml) of amber glass bottles closed with white PP child-proof screw caps. One bottle with a double-ended, polystyrene dosing spoon is packed in cardboard box. The dosing spoon is calibrated to measure 2.5 ml and 5 ml volumes.

The excipients used in the finished product are propylene glycol, liquid (non-crystallising) sorbitol, anhydrous citric acid, sodium citrate, sodium cyclamate, hypromellose (type 2910), disodium edetate, almond flavor (which contains propylene glycol, heliotropine, benzaldehyde, vanillin, acetophenone, anisyl alcohol, anisaldehyde, dihydrocoumarin) and purified water. All excipients used comply with their respective Ph. Eur. monograph, except almond flavour which complies with the manufacturer specification as well as with the EU regulation (EC/1334/2008) on food flavouring. Compliance of the product with the general monograph of the Ph. Eur. on *the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Conference on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis of the batches are presented.

The container closure system of the product consist of amber glass bottles (in three different sizes: 60, 125 and 150 ml) closed with white PP child-proof screw caps. One bottle with a double-ended polystyrene dosing spoon is packed in cardboard box. The dosing spoon is calibrated to measure 2.5 ml and 5 ml volumes. Specifications and quality certificates for all packaging components are enclosed. Certificates of analysis justifying the conformity to the relevant monograph of the Ph. Eur. are provided.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 24 months is approved with the following storage condition: “Store in the original package, in order to protect from light. This medicinal product does not require any special temperature storage conditions”.

The in-use stability of the drug product over 4 weeks after first opening is demonstrated**.**

The SmPC, Patient Information Leaflet (PIL) and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end

of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical point of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This is a generic application of desloratadine 0.5 mg/ml oral solution.

Pharmacodynamic, pharmacokinetic and toxicological properties of desloratadine are well known. As desloratadine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

III.2 Pharmacology

Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H_1-receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H_1-receptors because the substance is excluded from entry to the central nervous system.

III.3 Pharmacokinetics

Desloratadine was generally well absorbed with oral bioavailability of 45-94% observed in rats and monkeys.

The metabolism of desloratadine is comparable to its parent compound, loratadine, which is primarily metabolized to desloratadine via removal of carboethoxy group. This compound is further metabolized, and the metabolites are excreted unchanged as glucuronides or as further oxidized and conjugated products.

Faecal excretions the primary route of elimination, although a significant portion is also excreted in the urine following the oral administration.

III.4 Toxicology

Non-clinical data with desloratadine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

The lack of carcinogenic potential was demonstrated in studies conducted with desloratadine and loratadine.

III.5 Ecotoxicology/environmental risk assessment

Since Lordestin 0.5 mg/ml oral solution is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

The pharmaco-toxicological properties of desloratadine are well-known. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to desloratadine. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application for a marketing authorisation, submitted by Gedeon Richter Plc. *via* Decentralised Procedure with Hungary as RMS, concerns an abridged application according to the article 10.1 of the Directive 2001/83/EC (i.e. a generic application, the reference product is Aerius 0,5 mg/ml oral solution from Schering-Plough (authorised since 2001 in the EU) for Lordestin 0.5 mg/ml oral solution.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Desloratadine plasma concentrations can be detected within 30 minutes of desloratadine administration in adults and adolescents. Desloratadine is well absorbed with maximum concentration achieved after approximately 3 hours; the terminal phase half-life is approximately 27 hours. The degree of accumulation of desloratadine was consistent with its half-life (approximately 27 hours) and a once daily dosing frequency.

In a series of pharmacokinetic and clinical trials, 6% of the subjects reached a higher concentration of desloratadine. The prevalence of this poor metaboliser phenotype was comparable for adult (6%) and paediatric subjects 2- to 11-year old (6%), and greater among Blacks (18% adult, 16% paediatric) than Caucasians (2% adult, 3% paediatric) in both populations.

Similar pharmacokinetic parameters were observed in a multiple-dose pharmacokinetic study conducted with the syrup formulation in paediatric poor metaboliser subjects 2- to 11-year old diagnosed with allergic rhinitis. The exposure (AUC) to desloratadine was about 6-fold higher and the C_{max} was about 3 to 4 fold higher at 3-6 hours with a terminal half-life of approximately 120 hours.

Desloratadine is moderately bound (83% - 87%) to plasma proteins. There is no evidence of clinically relevant active substance accumulation following once daily adult and adolescent dosing of desloratadine (5 mg to 20 mg) for 14 days.

The enzyme responsible for the metabolism of desloratadine has not been identified yet, and therefore, some interactions with other medicinal products cannot be fully excluded. Desloratadine does not inhibit CYP3A4 *in vivo,* and *in vitro* studies have shown that the medicinal product does not inhibit CYP2D6 and is neither a substrate nor an inhibitor of P-glycoprotein.

In a single dose trial using a 7.5 mg dose of desloratadine, there was no effect of food

(high-fat, high caloric breakfast) on the disposition of desloratadine. In another study, grapefruit juice had no effect on the disposition of desloratadine.

IV.2.2 Biowaiver

Based on the *Guideline on the investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 rev. 1/Corr, London, 20 January 2010), a biowaiver is applicable for the test product. Aqueous solutions of similar composition are taken as bioequivalent without further comparative bioavailability studies.

IV.3 Pharmacodynamics

Desloratadine has demonstrated antiallergic properties in *in vitro* studies. These include inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8, and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells. The clinical relevance of these observations remains to be confirmed.

IV.4 Clinical efficacy

The efficacy of desloratadine has already been demonstrated during the clinical development of the reference product. No new data have been submitted.

IV.5 Clinical safety

The clinical safety of desloratadine has been well established. There was no need for submission of new data.

IV.6 Pharmacovigilance

IV.6.1 Pharmacovigilance system

The applicant submitted the Summaries of Pharmacovigilance System master file of the proposed marketing authorisation holders in the RMS and CMSs which contains all of the elements which is required According to the Article 8.3(ia) of the 2001/83/EC Directive as amended.

IV.5.2 Risk Management Plan

The next Table summarises the proposed pharmacovigilance activities and proposed risk minimisation activities as presented by safety concern.

Safety concern	*Routine risk minimisation measures*	*Additional risk minimisation measures*
Important identified risks		
Hypersensitivity	Appropriate labelling (SmPC and PIL)	No additional risk minimisation activities are planned
Important potential risks		
Severe renal insufficiency	Appropriate labelling (SmPC and PIL)	No additional risk minimisation activities are planned
Important missing information		
Use in pregnancy	Appropriate labelling (SmPC and PIL)	No additional risk minimisation activities are planned
Use during breast-feeding		
Use in children below the 1 year of age		

IV.6.3 Periodic Safety Update Reports

Periodic Safety Update Reports (PSUR) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the Data Lack Point and frequency of submission of the next PSUR.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

For these applications establishment of the bioequivalence described in section IV.2 is pivotal.

The product has been shown to be essentially similar and refer to a product approved on the basis of a full application with regard to clinical efficacy/safety data. No further such studies have been submitted or are considered necessary. There is no concern about granting of the marketing authorisation from clinical points of view.

V. Overall conclusion, benefit/risk assessment and recommendation

V.1 Summary

The present applications concern Lordestin 0.5 mg/ml oral solution. The applicant and the future holder of authorisation is Gedeon Richter Plc. (Hungary).

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator product was Aerius 0.5 mg/ml oral solution from Schering-Plough authorised for marketing since 2001 in the European Union. Bioequivalence between the originator and the submitted products was established on the basis of an adequate biowaiver.

Lordestin 0.5 mg/ml oral solution is indicated for in adults, adolescents and children over the age of 1 year for the relief of symptoms associated with allergic rhinitis and urticaria.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Lordestin 0.5 mg/ml oral solution.

V.2 Classification

Prescription-only medicine

V.3 Package Leaflet and user consultation

The package leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non-approval	Assessment report attached