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M E B

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lactulosestroop Actavis 667 mg/ml, syrup
Actavis Group PTC ehf, Iceland

lactulose

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1737/001/MR
Registration number in the Netherlands: RVG 102789

8 April 2010

Pharmacotherapeutic group:	laxatives, osmotically acting laxatives
ATC code:	A06AD11
Route of administration:	oral
Therapeutic indication:	constipation
Prescription status:	non prescription
Date of first authorisation in NL:	19 August 2008
Concerned Member States:	Mutual recognition procedure with DE, FI, MT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Lactulosestroop Actavis 667 mg/ml, syrup from Actavis Group PTC ehf. The date of authorisation was on 19 August 2008 in the Netherlands. The product is indicated for treatment of constipation.

A comprehensive description of the indications and posology is given in the SPC.

Lactulose, a disaccharide of galactose and fructose, is an osmotic laxative. It is a synthetic disaccharide that is not digested in the small intestine and not absorbed since the specific disaccharidase is lacking in humans. It passes unchanged into the colon where it serves as an energy source for the carbohydrate-splitting bacteria. During this process short chain fatty acids are formed, the main degradation products being acetic acid, lactic acid, hydrogen and carbon dioxide. These acids lower the pH in the lumen and increase the osmolality of the intestinal contents. Stool volume is increased by moderate water retention in the intestine and intestinal peristalsis is enhanced and the passage through the colon is accelerated.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Duphalac syrup 667 mg/ml (NL License RVG 01467) which has been registered in the Netherlands by Solvay Pharma B.V. since 14 April 1982. In addition, reference is made to Duphalac authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. A bioequivalence study is not applicable, as Lactulose syrup is a liquid preparation and lactulose is not absorbed. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is lactulose, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Lactulose is a synthetic disaccharide. It is a reducing sugar crystallising in the a form; it is a transparent and sweet aqueous syrup containing lactulose to a concentration of 50% w/w (67% w/v) approximately (= 667 mg lactulose per ml = 500 mg per gram).

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. The specification is acceptable in view of the statements on the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance
The active substance is stable for 2 years when stored under the proposed conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM. The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Lactulosestroop Actavis 667 mg/ml is a clear solution. Each ml also contains not more than 100 mg of galactose, not more than 66,7 mg of lactose and not more than 6,7 mg of fructose.

The syrup is packed in white HDPE bottles of 200, 300, 500 or 1000 ml with PE screw-on cap and a PP measuring cup.

The product does not contain excipients.

Pharmaceutical development
The composition of the drug product is identical to the innovator product so no development or clinical studies were done. This is acceptable as it concerns an oral solution without excipients.

To the commercial package of the HDPE bottles, a measuring cup is added. For the measuring cups validation data of measuring 2.5, 5, 15 and 30 ml syrup with this cup are included in the dossier and compliance was shown with the Ph.Eur. 2.9.27 Uniformity of mass of delivered doses from multidose containers. Lactulose syrup is self-preservative due to the high sugar content (>50%), so no preservatives are necessary. The final product is microbiologically tested at release and shelf life in accordance with the Ph.Eur. monograph for lactulose liquid.

Manufacturing process
The manufacturing process consists of filling bottles with the active liquid. Sufficient validation data have been presented and the manufacturing process is adequately controlled.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, total sugars, relatively density, deliverable volume, uniformity of mass of delivered dose, microbiological purity. The specifications applied are in line with the Ph.Eur. monograph for lactulose liquid and liquid preparations for oral use. The analytical methods are in line with the Ph.Eur. monograph and therefore require no additional validation.
Batch analytical data have been provided on 3 batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on 3 batches of each strength stored at 25°C/60% RH (24 months), 30°/65% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies were according to the ICH stability guideline. The batches were stored HDPE bottles. A shelf-life of 24 months was granted, when stored below 25°C.
Stability data has been provided demonstrating that the product remains stable for 2 months following first opening, when stored at room temperature.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Duphalac lactulose, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of lactulose released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Lactulose has been used for more than 20 years as an osmotic laxative in the treatment of constipation. It is a synthetic disaccharide that is not digested in the small intestine. No new clinical data have been provided or are required. The pharmacology, pharmacokinetics and toxicology of the active substance is well known. The clinical expert report adequately summarises the published literature on Lactulose.
The sought indication and dose recommendations are the same as approved for the innovator product Duphalac in the Netherlands. Therefore, the benfit/ risk balance of this formulation should be considered similar to that of the innovator.

Pharmacokinetics

The quantitative and qualitative composition of the products at issue is identical to that of the innovator product Duphalac. No bio-equivalence study has been performed or is required, since the product at issue is a liquid preparation and lactulose is not intended to be absorbed.

Risk management plan

Lactulose was first approved in 1964, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of lactulose can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

At the start of the procedure, the SPC text was in line with the MRP SPC of Latulose Alternova 667 mg/ml syrup, NL/H/0682/001. During the procedure, the MAH updated the SPC to a large extent in line with UK/H/1552/001/MR, as proposed by the member states. This procedure was approved on 30 July 2009 in 17 countries, and is more recent than NL/H/0682/001 (approved on 20 January 2006 in NL, FI, SE).

Readability test

The package leaflet 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. Prior to testing the PIL was rewritten by the authors of the readability test report. The test consisted of two rounds with 10 participants each. The respondent groups were checked for an adequate distribution of the parameters sex, age and education. Twelve questions were asked, sufficiently addressing the key safety messages. Additional remarks regarding a number of aspects of layout and content made by the respondents were noted as well.

Results of the first round of testing were good overall. For all items at least 90% were able to find the information requested and at least 90% showed that they understood and acted upon it. After the first test round no critical issues could be identified, therefore the package leaflet was not changed. Results of the second round of testing confirmed the results of the first test round: at least 90% of the respondents scored well on all of the diagnostic questions. General impressions of the respondents were positive. Most respondents' first impression was that it is a very clear and conveniently arranged package leaflet, which is easy to read. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lactulosestroop Actavis 667 mg/ml, syrup has a proven chemical-pharmaceutical quality and is a generic form of Duphalac 667 mg/ml. Duphalac is a well-known medicinal product with an established favourable efficacy and safety profile.

No bioequivalence study was deemed necessary, as Lactulosestroop Actavis 667 mg/ml is a liquid preparation and lactulose is not absorbed.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other lactulose containing products.

The Board followed the advice of the assessors. Lactulosestroop Actavis 667 mg/ml, syrup was authorised in the Netherlands on 19 August 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lactulosestroop Actavis 667 mg/ml, syrup with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 2 December 2009.

A European harmonised birth date has been allocated (21 May 1964) and subsequently the first data lock point for lactulose is May 2011. The first PSUR will cover the period from December 2009 to May 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 2 December 2014

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached