

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Lactulose Sandoz 670 mg/ml, syrup
Sandoz B.V., the Netherlands**

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/2325/001/DC
Registration number in the Netherlands: RVG 109594**

7 November 2012

Pharmacotherapeutic group:	laxatives, osmotically acting laxatives
ATC code:	A06AD11
Route of administration:	oral
Therapeutic indication:	constipation
Prescription status:	non prescription
Date of authorisation in NL:	24 September 2012
Concerned Member States:	Decentralised procedure with BE, DK, EE, FI, LT, LV, PT, RO, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

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 Lactulose Sandoz 670 mg/ml, syrup from Sandoz B.V. The date of authorisation was on 24 September 2012 in the Netherlands. The product is indicated for symptomatic 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 decentralised procedure concerns a hybrid 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 Abbott B.V. since 14 April 1982 (original product). In addition, reference is made to Duphalac authorisations in the individual member states (reference product). It concerns a hybrid application, as the strength differs from the innovator.

The marketing authorisation is granted based on article 10(3) 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.*). It is a clear solution with pH 3.0 – 7.0.

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 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

Lactulose, liquid is tested according to the European Pharmacopoeia, current edition. The test for boron and methanol as basically required in the Ph.Eur. monograph were omitted since neither substance is used in the production process. Batch analytical data demonstrating compliance with the specification have been provided for 3 batches.

Stability of drug substance

Stability data on the active substance have been provided for 3 batches stored for 36 months at 25°C/60%RH and 18 months at 30°C/70%RH. A retest period could be granted of 2 years when stored below 30°C.

* *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

Lactulose Sandoz 670 mg/ml, syrup is a clear colourless to pale brownish yellow, viscous solution. 1 ml contains 670 mg lactulose (as lactulose liquid).

The syrup is packed in brown or white PET bottles with polyethylene screw cap or polypropylene closure, or brown glass bottles with polyethylene screw cap. As measuring device a measuring cup (polypropylene) with filling marks at 5, 10, 15, 20, 25 and 30 ml is added.

The product does not contain excipients.

Pharmaceutical development

The pharmaceutical development of the drug product has been adequately performed. As the formulation is an aqueous solution for oral use without any excipients, the omission of a bioequivalence study is acceptable. The omission of formulation or manufacturing process development is acceptable. The suitability of the container closure system has been demonstrated by means of extractable studies,

closure tightness and agglutination and testing of the accuracy of the measuring device at different volumes. The results are acceptable. Although the drug product is a multi-dose preparation, no preservative has been added. This is acceptable as the self-preserving characteristics of the formulation has been demonstrated.

Manufacturing process

The description of the standard manufacturing process is sufficient and concerns filling of the non-sterile filtered bulk active substance into bottles only. The in-process controls are adequately described. As the drug product is not sterile, the specifications of the drug substance and the drug product are considered to be sufficient for the control of the manufacturing process. Thereby, the omission of validation data can be accepted.

Quality control of drug product

The product specification includes tests for identification, filling volume, characters, appearance, pH, related substances, sulphites, lead, sulphated ash, lactulose assay and microbial contamination. The specification for the finished product is acceptable.

All methods performed for testing the quality on „Lactulose, Liquid“ and their validations have been approved by the Council of Europe - European Department for the Quality of Medicines. Batch analysis data have been presented for full-scale batches packed in brown glass bottles, brown PET bottles and white PET bottles, demonstrating compliance with the specifications.

Stability of drug product

Stability data have been provided on the drug product stored in PET bottles and glass bottles at 25°C/60% RH (up to 36 months), 30°C/70% RH (up to 18 months) and 40°C/75% RH (6 month).

No photostability study has been included. The drug product is packed in brown or white bottles that are all specified for transparency (NMT 10%). The light-protecting nature of the glass and PET bottles is thereby considered to be sufficiently controlled.

A shelf life of 36 months for the preparation packed in different containers can be accepted with a storage condition of 'store below 25°C'. After first opening an in-use shelf-life of 12 months is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactulose used in the synthesis of the drug substance is of animal origin manufactured in line with the applicable Note for Guidance of the EMA.

II.2 Non-clinical aspects

This product is a hybrid formulation of Duphalac lactulose which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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 benefit/risk balance of this formulation is considered similar to that of the innovator.

Pharmacokinetics

The qualitative composition of the products at issue is the same as that of the innovator product Duphalac. No bioequivalence 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 post authorisation 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

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Duphalac.

Readability test

The package leaflet has not been evaluated via a user consultation study. Instead, a bridging report to the successfully user tested PL of Laevolac 200 ml has been provided. The bridging report is satisfactory.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lactulose Sandoz 670 mg/ml, syrup has a proven chemical-pharmaceutical quality and is a hybrid form of Duphalac syrup 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 Lactulose Sandoz 670 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lactulose Sandoz 670 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 July 2012. Lactulose Sandoz 670 mg/ml was authorised in the Netherlands on 24 September 2012.

The date for the first renewal will be: 23 June 2015.

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 _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

