Bundesamt für Sicherheit
im Gesundheitswesen

Public Assessment Report

Scientific discussion

Lactulose „Fresenius“ 670 mg/ml Lösung zum Einnehmen

Lactulose

AT/H/0383/001/MR

This module reflects the scientific discussion for the approval of Lactulose Fresenius. The procedure was finalised on 06.09.2010. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

The active ingredient of “Lactulose “Fresenius” 670 mg/ml Lösung zum Einnehmen” is lactulose - a synthetic disaccharide sugar. Lactulose is an osmotically acting laxative and is indicated for the symptomatic treatment of constipation, found to be refractory to high-roughage diet or other general measures, as well as diseases requiring easy defecation and also for the treatment of portal systemic encephalopathy. “Lactulose “Fresenius” 670 mg/ml Lösung zum Einnehmen” is to be taken orally, but acting locally and exerts its effect within the colon. The recommended dosages are to be adapted to the requirements of the individual patients according to the severity and development of their condition. There are empirical experiences for years on the market with numerous lactulose preparations as e.g. syrup. The product is marketed in Austria in an identical formulation since years.

Lactulose “Fresenius” 670 mg/ml Lösung zum Einnehmen is essentially similar to the earlier in Austria approved Duphalac-Sirup. The application is an abridged application. It is submitted under article 10 (1) (essentially similar product) of Directive 2001/83/EC. It is managed through the Mutual Recognition Procedure with Austria as Reference Member State.
Duphalac-Sirup was authorised in Austria in 1968.

II. QUALITY ASPECTS

II.1 Introduction

Lactulose Fresenius is an oral solution which is presented in brown glass bottles with polyethylene / polypropylene closures, brown PET-bottles with polyethylene / polypropylene closures or white PET-bottles with polyethylene / polypropylene closures.

II.2 Drug Substance

The active substance in Lactulose Fresenius is lactulose as lactulose liquid. The specification of the active substance/s meets the current scientific requirements. The adequate quality of the active substance has been shown by submitting the appropriate control data. The stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.
The quality of the drug substance is guaranteed by the certificate of suitability (R1-CEP 1998-130-Rev 03).

II.3 Medicinal Product

Lactulose Fresenius contains no excipients:

The manufacturer responsible for batch release is:
Fresenius Kabi Austria GmbH
Estermannstrasse 17
4020 Linz, Austria

The development of the product has been sufficiently made and deemed appropriate. The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.
The packaging of the medicinal product complies with the current legal requirements.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 36 months when stored below 25°C.

The pharmaceutical quality of Lactulose Fresenius has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Lactulose are well known. As Lactulose is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

Lactulose is a synthetic disaccharide formed from D-galactose and fructose. In the colon lactulose is metabolised by bacterial enzymes to short chained fatty acids mainly lactic and acetic acid as well as methane and hydrogen. This effect leads to a decrease of the pH-value and an increase of the osmotic pressure in the colon. This causes stimulation of peristalsis and an increase of the water content of the faeces.
In higher dosage lactulose causes a reduction of the pH-value, which results in an increased H+-concentration and a shift from NH_3 (absorbable) to NH_4^+ (non-absorbable). The nitrogen excretion in the stool is accelerated. This effect may be used in the treatment of hyperammonaemia. In the treatment of hepatic encephalopathy lactulose reduces the concentration of NH_3 in the blood by about 25-50 %.
Pharmacokinetic:
Lactulose is practically not absorbed, because in man there is no corresponding disaccharidase available in the upper intestinal tract. Not being absorbed as such, it reaches the colon unchanged. There it is metabolised by the colonic bacterial flora. Metabolism is complete at doses up to 25-50 g or 40-75 ml; at higher dosages, a proportion may be excreted unchanged.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The pharmaceutical quality of Lactulose Fresenius has been adequately shown.
The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.
The application contains an adequate review of published clinical data.

User consultation

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. The language used for the purpose of user testing the PIL was English.
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.