LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lopacut
(loperamide hydrochloride)

SE/H/817/01/DC

This module reflects the scientific discussion for the approval of Lopacut. The procedure was finalised at 2010-10-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Vitabalans Oy has applied for a marketing authorisation for Lopacut, 2 mg, film-coated tablet, claiming essential similarity to Imodium, 2 mg, tablet, marketed in Sweden by McNeil Sweden AB. The product contains loperamide as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Imodium, 2 mg, hard capsule, marketed by Mc Neil in Finland.

II. QUALITY ASPECTS

II.1 Introduction

Lopacut is presented in the form of film-coated tablets containing 2 mg of loperamide hydrochloride. The excipients are microcrystalline cellulose, croscarmellose sodium, magnesium stearate, pregelatinised maize starch, colloidal anhydrous silica and the tablet coating blend containing hypromellose, macrogol, polydextrose and titanium dioxide. The tablets are packed in PVC/Al blisters.

II.2 Drug Substance

Loperamide hydrochloride has a monograph in the Ph. Eur.

Loperamide hydrochloride is a white or almost white powder. It is slightly soluble in water, freely soluble in alcohol and in methanol. The structure of loperamide hydrochloride has been proven and its physico-chemical properties described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Lopacut film-coated tablets are formulated using excipients described in the current Ph. Eur., except for the coating blend which is controlled according to acceptable in house specifications. No materials of animal and/or human origin are contained or used in the manufacturing process of the medicinal product.

The manufacturing process has been sufficiently described and validated. The tests and limits in the specification are considered appropriate to control the quality of the finished product.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Following oral administration, loperamide is well absorbed but undergoes substantial first pass extraction, and the systemic levels are therefore low. The half-life is in the range 9-14 hours and elimination occurs via oxidative N-demethylation. Unchanged loperamide and metabolites are mainly excreted in faeces. There is no restriction with respect to food in the labelling for the originator product.

To support the application, the applicant has submitted as report a single-centre, single-dose, randomised, 2-way cross-over bioequivalence study (Clinical study report V-807), in which Lopacut 2x2 mg tablets are compared with the originator Imodium 2x2 mg tablets from the Finnish market following a single dose under fasting conditions in healthy volunteers. Bioequivalence between Lopacut and Imodium can be concluded and the results are shown below.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Lopacut tablet 2x2 mg	**14.120 ± 6.7307**	**0.817± 0.3851**	**2.025 (0.500 – 7.030)**
Imodium capsule 2x2 mg	**15.321± 9.2438**	**0.894± 0.6000**	**2.000 (0.550 – 7.000)**
***Ratio (90% CI)**	**96.4 (84.8 – 109.5)**	**96.6 (85.5 – 109.2)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated using ln-transformed values*

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 Czech.
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.

The risk/benefit ratio is considered positive and Lopacut, 2 mg, film-coated tablet, is recommended for approval.

VI. APPROVAL

The decentralised procedure for Lopacut, 2 mg, film-coated tablet, was successfully finalised on 2010-10-14.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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