LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Cliovelle, tablets 1 mg/0.5 mg
(estradiol valerate/norethisterone acetate)

SE/H/657/01/E01

This module reflects the scientific discussion for the approval of Cliovelle. The procedure was finalised at 2009-02-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Dr Kade Pharmazeutische Fabrik GmbH has applied for a repeat use mutual recognition procedure aiming for marketing authorisation of Cliovelle tablets 1 mg/0.5 mg estradiol valerate/norethisterone acetate in DK, FI, and NO, and with SE as reference member state. The application is based on bibliographical data and on well established use referring to the Commission Directive 2001/83/EC. Cliovelle was approved for marketing in Sweden 2006-02-03. A Mutual Recognition Procedure with DE and PL was finalised on 2007-02-21.

Cliovelle is a continuous combined oestrogen-progestogen hormone replacement therapy (HRT) containing 1 mg estradiol (E2) valerate and 0,5 mg norethisterone acetate. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Cliovelle 1 mg/0.5 mg tablet is presented in the form of tablets containing 1.31 mg of estradiol valerate which corresponds to 1 mg of the estradiol and 0.5 mg of norethisterone acetate. The excipients are magnesium stearate, copovidone, maize starch and lactose monohydrate. The tablets are packed in blisters of polypropylene or PVC/PVDC/Aluminium.

II.2 Drug Substance

Both estradiol valerate and norethisterone acetate have monographs in the Ph Eur.

Estradiol valerate is a white or almost white powder and norethisterone acetate is a white or yellowish-white, crystalline powder that shows polymorphism. Both substances are practically insoluble in water. The structure of each of the drug substances has been adequately proved and its physicochemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substances specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Long term stability studies under ICH conditions have been conducted and accelerated data have also been provided. The data are sufficient to confirm the retest periods.

II.3 Medicinal Product

Cliovelle 1 mg/0.5 mg tablet is formulated using excipients described in the current Ph Eur. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physicochemical characteristics of the active substances.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

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

Estradiol and norethisterone acetate have well known pharmacological, pharmacokinetic and toxicological effects, adequately summarised in the non-clinical overview. No concerns for human safety can be anticipated based on the non-clinical documentation of the product.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The human pharmacokinetic documentation for Cliovelle consists of one bioequivalence study with Activelle as comparator. The study was of single-dose, randomised, 2-way, cross-over group-sequential design. After inclusion of twenty-four healthy postmenopausal females, an interim analysis was performed. Another 12 subjects were to be enrolled if bioequivalence could not be concluded based on the initial 24 subjects, but this was not needed, though. The statistical methods were adapted in accordance with the choice of study design. With the inclusion of 24 individuals, the 96.7% confidence intervals for the comparisons of Cliovelle vs. Activelle were contained within the interval of 80-125% for C_{max}, $AUC_{0-\infty}$ and AUC_{0-t} for both estradiol, estrone and norethisterone. Bioequivalence could therefore be concluded. Based on this, published data for Activelle can be extrapolated to this product.

IV.2 Clinical efficacy and safety

The clinical efficacy and safety of 1mg estradiol (E2) valerate and 0,5mg norethisterone acetate is well established as a product with similar contents is already approved for HRT and on the market in Europe (Activelle, 1mg estradiol (E2) hemihydrate; 0,5mg norethisterone acetate) since several years.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed and is acceptable.

The risk/benefit ratio is considered positive and Cliovelle, 1mg/0.5mg tablet is recommended for approval.

VI. APPROVAL

The repeat use Mutual recognitions for Cliovelle, 1 mg/0.5mg tablet was successfully finalised on 2009-02-27.

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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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