LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kodein E Consult
(codeine phosphate hemihydrate)

Asp no: 2013-1154

This module reflects the scientific discussion for the approval of Kodein E Consult. The procedure was finalised at 2014-08-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

E Consult ApS has applied for a marketing authorisation for Kodein E Consult, 25 mg, tablet. The application is submitted in accordance with Directive 2001/83/EC Article 10a, so called well-established use (WEU) application. For a WEU application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use.

In a WEU application, results of pre-clinical and clinical trials are replaced by detailed references to published scientific literature.

The active substance is codeine phosphate hemihydrate.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

The Codeine phosphate hemihydrate tablets are presented in the form of tablets containing 25 mg of codeine phosphate hemihydrate. The excipients are lactose monohydrate, potato starch, microcrystalline cellulose, talc, gelatine, magnesium stearate and hydrochloric acid. The tablets are packed in HDPE containers with a screw cap.

II.2 Drug Substance

Codeine phosphate hemihydrate has a monograph in the Ph. Eur.

Codeine phosphate hemihydrate is a white, crystalline powder or small colorless crystals which is freely soluble in water, slightly soluble or very slightly soluble in ethanol (96 %), practically insoluble in chloroform and ether. The structure of codeine phosphate hemihydrate has been adequately proven and its physico-chemical 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 substance specification includes relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

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

II.3 Medicinal Product

Codeine phosphate hemihydrate tablets are formulated using excipients described in the current Ph. Eur. All raw materials used in the product are of vegetable origin or has 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 physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of codeine phosphate hemihydrate are well known. As codeine is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Discussion on the non-clinical aspects

There are no objections to approval of Kodein E Consult from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The pharmacokinetic, clinical efficacy and safety properties of codeine are well known. As codeine is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

IV.2 Pharmacokinetics

Orally administered codeine is rapidly and extensively (<85%) absorbed followed by extensive metabolism in the liver. Parent compound and metabolites are primarily excreted renally. Thus both renal and hepatic function may impact the pharmacokinetics of codeine.

IV.3 Pharmacodynamics

Both effect and safety of codeine are closely related to the patient´s capacity to metabolize codeine to morphine, and possibly, other active metabolites. The metabolism to morphine is catalyzed by the polymorphic enzyme CYP2D6. A poor metabolizer may not produce enough morphine to achieve an adequate analgesic effect, while ultrafast metabolizers are at risk of toxicity, including lethal effects. The distribution of the ultrafast metabolising variant of

CYP2D6 varies, from 40% in North Africa to 3% in Europe. It is not common for patients in Sweden to be aware of their metabolic status.

IV.4 Clinical efficacy and safety

Clinical efficacy and safety properties of codeine are well known. The 2013 paediatric dose recommendations from PRAC are included in the application.

IV.5 Discussion on the clinical aspects

There are no objections to approval of Kodein E Consult 25 mg tablet from a pharmacokinetics point of view.

There are no objections to approval of Kodein E Consult 25 mg tablet from a clinically efficacy-safety point of view.

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 Swedish.

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 Kodein E Consult, 25 mg, tablet is recommended for approval.

VI. APPROVAL

Kodein E Consult, 25 mg, tablet was approved in the national procedure on 2014-08-14.

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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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