LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Codalvonil
(paracetamol, codein phosphate hemihydrate)

SE/H/1121/01/DC

This module reflects the scientific discussion for the approval of Codalvonil. The procedure was finalised at 2012-02-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Meda AB has applied for a marketing authorisation for Codalvonil, efferverscent tablet, 500 mg/30 mg claiming essential similarity to Citodon, efferverscent tablet, 500 mg/30 mg marketed in Sweden by BioPhausia AB. The product contains paracetamol / codeine phosphate hemihydrates as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Citodon, efferverscent tablet, 500 mg/30 mg marketed by Biophausia AB in Sweden.

II. QUALITY ASPECTS

II.1 Introduction

The medicinal product Codalvonil is a white and round effervescent tablet containing 500 mg of the active ingredient Paracetamol and 30 mg of the active ingredient Codeine phosphate hemihydrate. The tablets are packaged in polypropylene tubes closed with polyethene stoppers. The stoppers are filled with desiccant material in order to protect the tablets from moisture.

II.2 Drug Substance

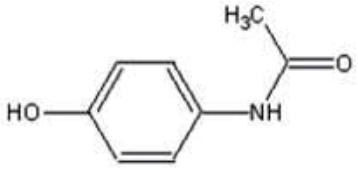
Codalvonil contains two drug substances; Paracetamol and Codeine phosphate hemihydrate. Both substances are controlled in accordance with a Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM). The certificates certify that the substances are controlled in accordance with the relevant monograph of the European Pharmacopeia (Ph. Eur.).

Statements from the Qualified Person (responsible for batch release of the finished product) have been presented, confirming that Paracetamol and Codeine phosphate hemihydrate are manufactured in compliance with the guidelines on Good Manufacturing Practise for active substances.

Paracetamol

International non-proprietary name (INN):	Paracetamol
United States Adopted Name (USAN):	Acetaminophen
Chemical names:	N-(4-Hydroxyphenyl)acetamide
CAS registry number:	103-90-2
Molecular formula:	$C_8H_9NO_2$
Relative molecular mass:	151.2 g/mol
Physical characteristics:	White or almost white, crystalline powder
Solubility:	Sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride
Melting point:	168 °C to 172 °C

Molecular structure:



Paracetamol is described in a monograph published in the European Pharmacopeia.

The drug substance specification includes relevant tests and the limits are acceptable. The specification fulfils the requirements of the European Pharmacopeia.

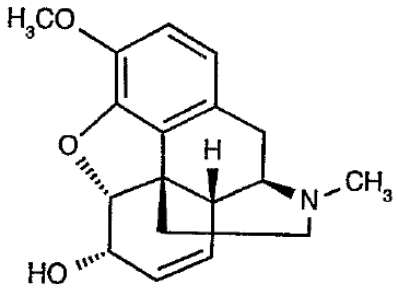
The analytical procedures are derived from the monograph “Paracetamol” of the European Pharmacopeia.

A re-test period of five years is specified in the Certificate of Suitability.

Codeine phosphate hemihydrate

International non-proprietary name (INN):	Codeine phosphate hemihydrate
Chemical names:	(5R,6S,9R,13S,14R)-3-Methoxy-17-methyl-4,5-epoxymorphin-7-en-6-ol-phosphate
Other name:	Codeini phosphas hemihydricus
CAS registry number:	41444-62-6
Molecular formula:	$C_{18}H_{24}NO_7P \cdot 0.5H_2O$
Relative molecular mass:	406.4 g/mol
Physical characteristics:	White or almost white, crystalline powder or small, colourless crystals
Solubility:	Freely soluble in water, slightly soluble or very slightly soluble in ethanol (96 per cent)

Molecular structure:



Codeine phosphate hemihydrate is described in a monograph published in the European Pharmacopeia.

The drug substance specification includes relevant tests and the limits are acceptable. The specification fulfils the requirements of the European Pharmacopeia.

The analytical procedures are derived from the monograph “Codeine phosphate hemihydrate” of the European Pharmacopeia. An additional test for residual ethanol is performed in accordance with the analytical procedure described in the Certificate of Suitability.

Stability studies have been conducted. The stability data support a re-test period of 36 months.

II.3 Medicinal Product

The medicinal product Codalvonil effervescent tablet is formulated using excipients described in the European Pharmacopeia, with the exception of Sodium dihydrogen citrate and the flavours. Sodium dihydrogen citrate is adequately controlled according to the Deutschen Arzneimittel-Codex (DAC) and acceptable in-house specifications have been established for the flavours. None of the ingredients are of animal or human origin.

The pharmaceutical development work has been sufficiently described. The reference medicinal product is Citodon 500 mg/30 mg effervescent tablets, marketed in Sweden by BioPhausia AB. The qualitative composition is identical and the amounts of Paracetamol and Codeine phosphate hemihydrate are the same. A clinical bioequivalence study has not been conducted given the compositional similarities and the fact that both products are aqueous solutions at the time of administration. A bioequivalence study waiver is considered acceptable from a pharmaceutical perspective.

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. It has been verified that the finished product is manufactured in accordance with Good Manufacturing Practise.

The release and shelf-life specifications are considered appropriate to control the quality of the finished product in relation to its intended purpose. The analytical procedures have been validated. Batch analysis data demonstrate that the product meets the requirements of the specification.

Stability studies under ICH conditions have been performed. The stability of the effervescent tablets was found satisfactory at all storage conditions. The stability data support a shelf-life of 36 months when stored in polypropylene tubes closed with polyethene stoppers containing a desiccant material. No additional storage advice is deemed necessary.

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

Pharmacokinetics
A comparison of the bioequivalence between Codalvonil effervescent tablets and Citodon effervescent tablets has not been performed since both products are aqueous oral solutions at the time of administration and contain the same active substances in the same concentrations. The products also contain the same excipients. A bioequivalence study comparing Codalvonil

with the originator Citodon can therefore be waived according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/**) Appendix II.

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 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.

The risk/benefit ratio is considered positive and Codalvonil, efferverscent tablet, 500 mg/30 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Codalvonil, efferverscent tablet, 500 mg/30 mg was successfully finalised on 2012-02-15.

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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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