HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY

Public Assessment Report

Scientific discussion

Codinep 10mg, 15mg, 20mg, 30mg tablets

(codeine phosphate hemihydrate)

HU/H/0608/001-004/DC

Date: 16.04.2026.

This module reflects the scientific discussion for the approval of Codinep 10 mg, 15 mg, 20 mg, 30 mg tablets. The procedure was finalised at 14-03-2019. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Codinep 10 mg, 15 mg, 20 mg, 30 mg tablets, from ExtractumPharma zrt.

The product is indicated for*:*

Codeine is indicated in adults and children older than 12 years of age for:
- treatment of acute moderate pain which is not relieved by other analgesics such as paracetamol or ibuprofen (alone)
- symptomatic relief of unproductive cough
- symptomatic relief of diarrhoea, after failure of loperamide.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC for the 10 mg and 20 mg tablets and Article 10(1) for the 15 mg and 30 mg tablets.

In this decentralised procedure, essential similarity is proven between the new product and the reference product Codeine Phosphate Tablets BP 15 mg (Bristol Laboratories Limited, UK).

The concerned member state (CMS) involved in this procedure was NL.

II. QUALITY ASPECTS

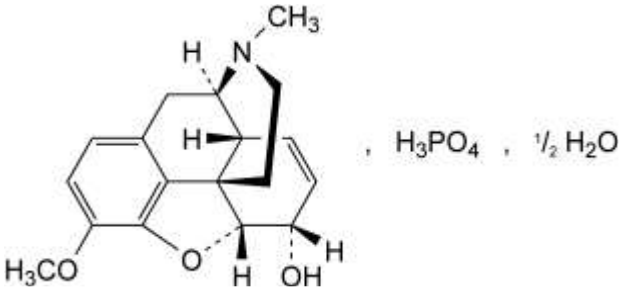
II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of CodigonEP 10 mg and 20 mg tablets via a decentralized procedure according to Article 10(3) of consolidated Directive 2001/83/EC (i.e. a hybrid application) as well as the application of CodigonEP 15 mg and 30 mg tablets via a decentralized procedure according to Article 10(1) of consolidated Directive 2001/83/EC (i.e. a generic application).
The products have been developed by ExtractumPharma.
The reference product is Codeine Phosphate BP tablets (containing 15 mg codeine phosphate as active ingredient) which were the original products of Bristol Laboratories, UK.

II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Codeine phosphate
Chemical name: 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate hemihydrate
Structure:



The active substance is white or almost white, crystalline powder or small, colourless crystals. It is freely soluble in water, slightly soluble or very slightly soluble in ethanol (96 per cent) and practically insoluble in chloroform and ether.

The substance is specified according to the requirements of the current Ph.Eur. monograph, additional specification has been set for appearance of the solution, additional specified impurity, residual solvents and microbiological quality. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.
Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.
A retest period and the packaging material (double polyethylene bag placed in a polyethylene drum) have been mentioned on the CEP.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim was to formulate tablets having essentially similar *in vitro* characteristics and *in vivo* performance with the Reference product Codeine Phosphate BP tablets (Bristol Laboratories, UK).
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.
10 mg tablets: White or almost white, oblong, both side convex tablets of 10 mm length, engraved with ’10’ on one side and scored on the other side. The tablet can be divided into equal doses.
15 mg tablets: White or almost white, round, flat-faced, bevelled-edge tablets of 7.5 mm diameter, engraved with ’15’ on one side and plain on the other side.
20 mg tablets: White or almost white, round, flat, bevelled-edge tablets of 8.5 mm diameter, engraved with ’20’ on one side and scored on the other side. The tablet can be divided into equal doses.
30 mg tablets: White or almost white, hexagonal, flat, bevelled-edge tablets of 9.5 mm diameter, engraved with ’30’ on one side and scored on the other side. The tablet can be divided into equal doses.

The excipients used in the finished product are microcrystalline cellulose, cellactose 80 (lactose monohydrate, cellulose powder), colloidal anhydrous silica, sodium starch glycolate and magnesium stearate. All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure systems of the product are clear, transparent PVC/PVdC//Alu blisters or white, opaque HDPE container with PP cap with desiccant and safety ring. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 12 months in PVC/PVdC//Alu blister is approved with the following storage restriction: “Store below 25 °C. Keep the blister in the outer carton in order to protect from light.” In HDPE container, a shelf-life of 24 months is approved when kept the container tightly closed in order to protect from light.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of codeine phosphate are well known. As codeine phosphate 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.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Based on these relevant documents ('Guideline on the environmental risk assessment of medicinal products for human use and ‘From the Questions and Answers on 'Guideline on the environmental risk assessment of medicinal products for human use') the Applicant provided consumption data of codeine. It is agreed that these data demonstrate a broadly steady consumption of codeine and it is unlikely that a significant increase in consumption will be generated. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

As codeine is a well-known active substance, new non-clinical studies were not performed and none were considered necessary. There are no objections to the granting of a marketing authorization from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview on the clinical pharmacology, efficacy and safety of the active substance of codeine is adequate.
For codeine the claimed indications and relevant clinical information are sufficiently supported by the submitted literature.

This application is a generic application, therefore, demonstration of therapeutic equivalence is shown by means of pharmacokinetic studies. No further clinical studies are required.

IV.2 Pharmacokinetics

One pivotal bioequivalence study has been reported in the submitted Dossier in order to support essential similarity between Codeine phosphate hemihydrate (CodigonEP) 15 mg film-coated tablets (Test Formulation, ExtractumPharma Ltd., Hungary) single oral dose and Codeine Phosphate Tablets BP 15 mg (Reference Formulation, Bristol Laboratories Limited, UK) single oral dose in healthy male and female volunteers under fasting conditions according to the bioequivalence guideline in force (*CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010*).

The applicant requested strength biowaiver for Codeine phosphate 10 mg, 20 mg and 30 mg tablets according to the General biowaiver criteria (*CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010*) and claiming linear pharmacokinetics of Codeine phosphate in the strength range 10-30 mg. The Applicant justified the linear pharmacokinetics of codeine.

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	115.0 ± 51.45	118.1 ± 51.33	39.8 ± 16.02	0.76 ± 0.263
Reference	112.8 ± 36.97	116.7 ± 37.19	43.3 ± 13.23	0.68 ± 0.240
***Ratio (90% CI)**	99.04 (93.81-104.57)	98.51 (93.55-103.73)	89.14 (81.61-97.38)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Both treatments were well tolerated, with no major side effects and no relevant differences in safety profiles. The 90% confidence intervals are within the normal acceptance range of 0.80 – 1.25 for AUC_t and C_{max}.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Codinep 15 mg tablets is considered bioequivalent with Codeine Phosphate Tablets BP 15 mg (Bristol Laboratories Limited, UK).

The results can be extrapolated to other strengths 10 mg, 20 mg, 30 mg tablets, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. It is also used in the treatment of cough and diarrhoea. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

IV.4 Clinical efficacy

No new clinical efficacy studies were presented and no such studies are required for this application.

IV.5 Clinical safety

No new clinical safety studies were presented and no such studies are required for this application.

IV.6 Risk Management Plan

Product's name: Codinep 10mg, 15mg, 20mg, 30mg tablets
Active substance: codeine phosphate hemihydrate
MAH: ExtractumPharma Co. Ltd.
Reference number: HU/H/0608/001-004/DC

1. Summary of Pharmacovigilance System

ExtractumPharma submitted a signed Summary of the ExtractumPharma's Pharmacovigilance System. Provided that the Pharmacovigilance System Master Files fully comply with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the Assessor considers the Summaries acceptable.

2. Risk Management Plan (version: 0.2, date of final sign off: 15.01.2019)

- **Summary of safety concerns**

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Considering that codeine phosphate has been marketed for a long period of time and the safety concerns are well characterised, not requiring further studies, moreover the reference product does not have an RMP and codeine is not listed in the "List of safety concerns per approved Risk Management Plan (RMP) of active substances per product (November 2018)" published on the HMA/CMDh site, the assessor is of the opinion that removal of all safety concerns is acceptable.

- **Pharmacovigilance Plan**

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to VENOPROTEP 500 mg film-coated tablets. No additional activities are proposed.

- **Risk Minimisation Measures**

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to VENOPROTEP 500 mg film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

3. PSUR

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.7 Discussion on the clinical aspects

This is an abridged application, no new clinical studies were conducted apart from a bioequivalence study. The application contains an adequate review of published clinical data and bioequivalence between the test and reference product has been adequately demonstrated.
There are no objections to approval of Codinep 10mg, 15mg, 20mg, 30mg tablets from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is adequate. Non-clinical part of the dossier based on literature review is appropriate. The application contains an adequate review of published clinical data and bioequivalence between the test and reference product has been adequately demonstrated.
Based on the review of the data on quality, efficacy and safety, the benefit-risk ratio for the product was considered positive.

Modul 6
Steps taken after the initial procedure with an influence on the Public Assessment Report

Procedure number	Type of modification [1]	Date of start of the procedure	Date of end of procedure	Approval/non approval
HU/H/0608/001-004/IB/001	B.II.f).1.b).1. As packaged for sale (supported by real time data)	2019.07.18	2019.08.17	Approved
HU/H/0608/003/IB/002	B.II.e).5.a).2. Change outside the range of the currently approved pack sizes	2019.07.18	2019.08.17	Approved
HU/H/0608/001-004/IA/003	B.III.1.a).3. New certificate from a new manufacturer (replacement or addition)	2019.09.12	2019.10.12	Positive
HU/H/0608/001-004/IB/004/G	B.I.b).2.e). Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate B.III.1.a).3. New certificate from a new manufacturer (replacement or addition)	2019.10.09	2019.11.08	Approved
HU/H/0608/001-004/IB/005	B.II.f).1.b).1. As packaged for sale (supported by real time data) Based on the generated stability data shelf-life extension request is submitted by the MAH for codeine phosphate hemihydrate containing products.	2020.01.23	2020.04.24	Approved
HU/H/0608/001-004/IB/006/G	B.III.1.a).2. Updated certificate from an already approved manufacturer	2023.07.13	2023.08.12	Approved

HU/H/0608/001-004/IA/007/G	A.4. Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites) B.I.a).1.f). Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place B.II.b).2.a). . Replacement or addition of a site where batch control/testing takes place B.III.1.a).2. Updated certificate from an already approved manufacturer	2024.02.09	2024.03.10	Positive
HU/H/0608/001-004/IB/008	B.II.f).1.b).1. As packaged for sale (supported by real time data)	2024.02.13	2024.03.14	Approved
HU/H/0608/001-004/IB/009/G	B.II.b).3.a). Minor change in the manufacturing process B.II.b).3.z). Other variation B.II.b).4.a). Up to 10-fold compared to the originally approved batch size B.II.b).5.z). Other variation	2024.10.07	2024.11.06	Approved
HU/H/0608/001-004/II/010	C.I.z). Other variation	2025.07.04	2026.01.19	Approved
HU/H/0608/001-004/IB/011	C.I.z). Other variation	2025.09.22	2026.02.27	Approved
HU/H/0608/001-004/IA/012/G	A.4. Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites) A.z). Other variation	2025.09.22	2025.10.22	Positive