IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Expudyne 250mg/5ml oral solution
Carbocisteine
PA23183/003/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Expudyne 250 mg / 5 ml Oral Solution, from JED Pharma Limited on 10th of March 2023 for a mucolytic agent indicated in adults and children 2 years and above for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus.

This is a generic product and the legal basis for this national procedure application is article 10 (1) of Directive 2001/83/EC as amended.

This medicinal product can be obtained without a prescription.

The Summary of Product Characteristics for (SmPC) and Patient Information Leaflet for this medicinal product is available on the HPRA's website.

Name of the product	Expudyne 250 mg / 5 ml Oral Solution
Name(s) of the active substance(s) (INN)	Carbocisteine
Pharmacotherapeutic classification (ATC code)	R05CB03- carbocisteine
Pharmaceutical form and strength(s)	Oral solution, 250/5 milligrams/millilitre
Marketing Authorisation Number(s) in Ireland (PA)	PA23183/003/001
Marketing Authorisation Holder	JED Pharma Limited
National Case No.	CRN00CHVC

II. QUALITY ASPECTS

II.1. Introduction
This application is for Expudyne 250 mg / 5 ml Oral Solution.

II.2 Drug substance
The active substance is carbocisteine, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product
P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances

All ingredients comply with the Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Expudyne 250 mg / 5 ml Oral Solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction
This active substance is a generic formulation of Mucodyne 250 mg/5 ml syrup oral solution on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology
N/A

III.3 Pharmacokinetics
N/A

III.4 Toxicology
N/A

III.5 Ecotoxicity/environmental risk assessment
Since Expudyne 250 mg/5 ml oral solution is a generic product, it will not lead to an increase exposure to the environment. Additional studies on environmental risk are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
Pharmacodynamic, pharmacokinetic and toxicological properties of carbocisteine are well known. As carbocisteine is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of application. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

Carbocisteine is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is comparable with that accepted for the reference and for similar products from other procedures. The reference product was Mucodyne syrup (PA0869/009/003) marketed by Ispen Pharmaceuticals Limited. Mucodyne syrup was withdrawn during the procedure. A new reference medical product was chosen as Muco Rhinathiol 5% sirop adultes (BE036811) marketed by Sanofi Belgium, to facilitate management of the product's life cycle in the post-authorisation phase.

For this generic application, the applicant was not required to perform bioequivalence studies in compliance with the CHMP guidance documents regarding oral solutions, (CPMP/PWP/EWP/1401/98 Rev 1/Corr**).

IV.2 Pharmacokinetics
No new PK studies were conducted to support this application.

Absorption
Carbocisteine is quickly absorbed from the gastrointestinal tract and reaches peak plasma levels in approximately 2 hours.

Distribution
The kinetics of the process follows a one-compartment model.

Metabolism
Metabolites are produced by acetylation and sulfoxidation decarboxylation. A diurnal variation in the metabolism of carbocisteine was seen.

Elimination
Elimination half-life is about 2 hours. Carbocisteine and its metabolites are excreted primarily through the kidneys.

IV.3 Pharmacodynamics
No new pD studies were conducted to support this application.
Carbocisteine (S-carboxymethyl L-cysteine) is a mucolytic agent that modifies mucous secretions. It acts during the gel phase of the mucus, most likely by breaking up the disulfide bonds of the glycoproteins, normalizing mucus hyperviscosity and thus favouring expectoration.

IV.4 Clinical Efficacy
No clinical efficacy data are provided as this is a generic application.

IV.5 Clinical Safety
As this is a generic application, no other clinical safety data are required.

A Risk Management Plan, version 0.1, dated 29th July 2021 has been submitted, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Carbocisteine 250mg/5ml sugar free oral solution. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

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.

IV.6 Discussion on the clinical aspects
As this approval concerns a generic application, there are no new efficacy or safety studies required, as the applicant can refer to the data of the reference medical products.

V. OVERALL CONCLUSIONS

Expudyne 250mg/5ml oral solution is a generic form of Mucodyne syrup 250mg/5ml, which is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence was waived in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product and similar licenced products.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Expudyne 250mg/5ml oral solution demonstrated a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

5 years from the finalisation of the procedure.

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	SmPC sections 1-9	10th March 2023	9th March 2028