IPAR

Public Assessment Report for a Medicinal Product for Human Use

Scientific discussion

Xtex 250 mg/5 ml oral solution
CARBOCISTEINE
PA0074/071/001

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.

CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Xtex 250 mg/5 ml oral solution, from Rowa Pharmaceuticals Limited on (date of authorisation) for the following indication:

Carbocisteine is a mucolytic agent for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus.
Xtex is indicated in adults and children aged 2 years and older.

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC and is referred to as a 'well-established use' application.

This medicinal product is not subject to medical prescription. Supply will be allowed through pharmacies only and this medicinal product can be promoted to the public.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.HPRA.ie

Name of the product	Xtex 250 mg/5 ml oral solution
Name(s) of the active substance(s) (INN)	CARBOCISTEINE
Pharmacotherapeutic classification (ATC code)	R05CB03
Pharmaceutical form and strength(s)	250 mg/5 ml oral solution
Marketing Authorisation Number(s) in Ireland (PA)	PA0074/071/001
Marketing Authorisation Holder	Rowa Pharmaceuticals Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Xtex 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 have been provided.

II.3 Medicinal product

P.1 Composition

Each 5 ml of the oral solution contains 250 mg of Carbocisteine Ph. Eur.

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 guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with the relevant monographs of the *European Pharmacopoeia*, where these exist, 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 'liquid preparations for oral use', 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 container complies with Ph. Eur. 3.2.1., 'Glass containers for pharmaceutical use', and that the measuring cup complies with directive 90/128/EEC relating to plastic materials intended to come into contact with foodstuffs.

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 Xtex 250 mg/5 ml oral solution.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC as a well-established use application.

No new non-clinical studies have been conducted and the studies reference are likely to predate GLP regulation standards.

III.2 Pharmacology

Carbocysteine is a mucolytic agent which dose dependently regularises the composition and consistency of mucus, making it more fluid and less viscous, whilst simultaneously stimulating mucociliary clearance.

No new studies have been submitted and the pharmacodynamics are discussed in the context of the mucoregulator activity of carbocysteine in a number of *in vivo* animal models.

No safety pharmacology studies have been described, however, their absence is superseded by the clinical experience with carbocysteine use.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies have been conducted. Carbocysteine is quickly absorbed after oral administration with low bioavailability of less than 10% and reaches pulmonary tissue and respiratory mucus two hours after administration.

III.4 Toxicology

No new non-clinical toxicity studies have been submitted. The toxicity profile of carbocysteine is well characterised in the published literature, and do not indicate any risk with respect to general toxicity or reproductive and developmental toxicity. No studies on genotoxicity or carcinogenicity have been found in the literature.

III.5 Ecotoxicity/environmental risk assessment

The justification for the absence of ERA studies is in line with the “Guideline On The Environmental Risk Assessment Of Medicinal Products For Human Use” (EMEA/CHMP/SWP/4447/00). Generic carbocisteine containing products have been available for almost 80 years. The introduction of an additional carbocisteine product to the market will not cause any significant increase in environmental exposure to the drug substance.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic, and toxicological properties of carbocysteine is well-known. As such, no new non-clinical data have been submitted by the applicant, and further non-clinical studies are not required. Overview based on literature review is appropriate. The non-clinical overview is exhaustive and sufficient to assess the relevant non-clinical aspects of the product. The overview has been written by an appropriately qualified person. The non-clinical overview is sufficient to support this marketing authorisation.

IV CLINICAL ASPECTS

IV.1 Introduction

Carbocisteine is a well-known active substances with established efficacy and safety.

The content of the SmPC approved during the national procedure is in accordance with that accepted for other similar medicinal products.

The applicant has submitted this application under Article 10a of Directive 2001/83/EC, “well-established use”. Applications under this article rely on bibliographic data to demonstrate the efficacy and safety profile of the active substance contained within the medicinal product, and as such no additional clinical studies are required. The bibliographic references provided by the applicant are sufficient for this purpose.

IV.2 Pharmacokinetics

Absorption

Carbocisteine is rapidly absorbed after oral administration. Peak plasma levels are reached 1 to 1.7 hours after oral administration.

Distribution
The kinetics of the process follows a one-compartment model. Carbocisteine has affinity for lung tissue and respiratory mucus, reaching maximum concentration in the mucus at 2 hours after oral administration.

Elimination
The plasma half-life of carbocisteine is 1.33 hours. The majority disposal occurs via the kidneys within 24 hours of administration, mainly as unchanged product (80%) or metabolites produced by acetylation and sulfoxidation decarboxylation. A small fraction is excreted in the faeces (0.3%) and pulmonary route.

IV.3 Pharmacodynamics

Goblet cells are the primary source of mucus production in the airways of the lungs. Studies in humans have demonstrated that carbocisteine reduces goblet cell hyperplasia. Carbocisteine can therefore be demonstrated to have a role in the management of disorders characterised by abnormal mucus.

IV.4 Clinical Efficacy

The applicant has provided several appropriate literature references demonstrating that the efficacy of carbocisteine is well established.

IV.5 Clinical Safety

The applicant has provided several appropriate literature references demonstrating that the safety of carbocisteine is well established. Undesirable effects listed in the SmPC are:

Gastrointestinal disorders:
Common: dyspepsia, nausea, vomiting, diarrhoea
They can occur especially at high doses. In these cases it may be useful to reduce the dose.
Rare: gastrointestinal haemorrhage

Nervous system disorders:
Rare: headache, dizziness

Skin and subcutaneous tissue disorders:
Rare: rash, pruritus
Very rare: fixed erythema

Immune system disorders:
Rare: hypersensitivity reactions
Very rare: bronchospasm

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan (RMP)

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities designed to identify, characterise, prevent or minimise risks relating to Xtex 250mg/5ml oral solution

The summary of safety concerns is presented below:

Summary of safety concerns	
Important identified risks	▪ Peptic ulcer ▪ Hypersensitivity
Important potential risks	▪ None
Missing information	▪ Use in pregnancy and lactation

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.
Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The schedule for the submission of PSUR reports is in accordance with that published in the EURD database on the HMA website, and as such is considered appropriate.

IV.6 Discussion on the clinical aspects

The clinical aspects of this medicinal product are well established and acceptable.

V OVERALL CONCLUSIONS

Xtex 250 mg/5 ml oral solution has a proven chemical-pharmaceutical quality and a well-established and favourable efficacy and safety profile. The applicant has appropriately demonstrated this profile using appropriate bibliographic references.

From a quality perspective the overall assessment outcome of Xtex 250 mg/5 ml oral solution is positive.

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 Xtex 250mg/5ml oral solution has demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VII UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE