

# **Public Assessment Report**

## **Scientific discussion**

**Paracetamol/Codeïne Eurogenerics  
500 mg/30 mg tablets  
(paracetamol and codeine phosphate  
hemihydrate)**

**NL/H/5828/001/DC**

**Date: 22 January 2026**

This module reflects the scientific discussion for the approval of Paracetamol/Codeïne Eurogenerics 500 mg/30 mg tablets. The procedure was finalised on 25 February 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

## List of abbreviations

ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Paracetamol/Codeïne Eurogenerics 500 mg/30 mg tablets, from Eurogenerics N.V.

The product is indicated for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone). Paracetamol/Codeïne Eurogenerics is indicated in patients older than 12 years of age.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and a European Reference Product (ERP), Dafalgan Codeine 500 mg/30 mg film-coated tablets, which has been registered by UPSA in Belgium (BE License number BE205886) since 18 October 1999. The justification to use this product is based on information received from Belgium.

The concerned member states (CMS) involved in this procedure were Belgium, Italy and Luxembourg.

## II. QUALITY ASPECTS

### II.1 Introduction

Paracetamol/Codeïne Eurogenerics is an uncoated immediate release tablet. The tablet is white to almost white, capsule-shaped and flat, with bevelled edge. It is debossed with 'PC2' on one side and a score line on the other side of the tablet. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Each tablet contains as active substances 500 mg of paracetamol and 22.1 mg of codeine (as 30 mg codeine phosphate hemihydrate).

The excipients are: pregelatinised maize starch, lactose monohydrate, talc (E553b), cellulose powdered (E460), povidone K30 (E1201), magnesium stearate (E572) and stearic acid (E570).

The tablets are packed in polyvinyl chloride (PVC)/aluminium blisters.

### II.2 Drug Substance

The drug substances are paracetamol and codeine phosphate hemihydrate, both are established active substances described in the European Pharmacopoeia (Ph.Eur.).

Paracetamol is a white or almost white crystalline powder. It is sparingly soluble in water, freely soluble in ethanol (96%) and very slightly soluble in methylene chloride. Codeine phosphate hemihydrate is a crystalline white powder and is freely soluble in water.

The CEP procedure is used for both active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

#### Manufacturing process

For both drug substances CEPs have been submitted; therefore no details on the manufacturing process have been included.

#### Quality control of drug substance

The active substance specifications are considered adequate to control the quality and meet the requirements of the monographs in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches per supplier of paracetamol and codeine phosphate hemihydrate.

#### Stability of drug substance

Paracetamol is stable for four years when stored under the stated conditions, codeine phosphate hemihydrate is stable for five years (or 60 months, depending on the supplier) when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

## **II.3 Medicinal Product**

#### Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The paediatric target population has been taken into account during the pharmaceutical development.

In order to support the BSC-based biowaiver, dissolution data at three pHs (1.2, 4.5 and 6.8) and in the QC medium pH 5.8, of the test product and reference product are compared showing that more than 85% of paracetamol and more than 85% codeine is released from the tablets within 15 min. in all tested media. Additionally the maximum single dose of the drug substance was dissolved in 250 ml buffer (pH 1.2, 4.5 and 6.8) and the solubility of the drug substances was measured up to saturation. In conclusion, codeine and paracetamol can both be classified as so called BCS-I drugs.

BCS-I drugs are pharmaceutical compounds classified under the Biopharmaceutics Classification System (BCS) as having high solubility and high permeability, meaning they

dissolve easily in water and pass readily through cell membranes, leading to good absorption in the body.

#### Manufacturing process

The manufacturing process comprises of two phases: manufacturing of paracetamol granules (intermediate) and manufacturing of tablets. The process is considered a standard process and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scaled batches in accordance with the relevant European guidelines.

#### Control of excipients

All excipients comply with the Ph.Eur. and functional related characteristics are discussed and included in the specifications of the excipients if relevant. These specifications are acceptable.

#### Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification of the active substances, water content, dissolution, assay, uniformity of dosage units by content uniformity, related substances of paracetamol, related substances of codeine, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided for three production scale batches, demonstrating compliance with the specification.

#### Stability of drug product

Stability data on the final product have been provided for two pilot scale batches stored at 25°C/ 60% RH (60 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Results of a photostability study indicate that the tablets are not sensitive to visible and UV light. On basis of the data submitted, a shelf life was granted of four years. No specific storage conditions needed to be included in the SmPC or on the label.

#### Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Paracetamol/Codeïne Eurogenerics has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Paracetamol/Codeïne Eurogenerics is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

### III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Dafalgan Codeine which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Paracetamol and codeine are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, and no bioequivalence studies were carried out. Instead, a BCS-based biowaiver was requested.

### IV.2 Pharmacokinetics

#### Biowaiver

The MAH has submitted a justification for a BCS-based biowaiver for Paracetamol/Codeïne Eurogenerics 500 mg/30 mg tablets with Dafalgan Codeine 500 mg/30 mg film-coated tablets as reference product.

A BCS-based biowaiver is applicable for an immediate release drug product if

- the drug substance has been proven to exhibit high solubility and complete absorption (BCS Class I) and
- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min ) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements and
- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

The dissolution was investigated according to the EMA Bioequivalence guideline. Based on the submitted data, paracetamol and codeine can be considered BSC Class I drugs. Comparative dissolution tests showed that test and reference product both dissolved very rapidly in all three media (≥85% in 15 minutes) in dissolution media pH 1.2, pH 4.5 and pH 6.8. The test and reference formulation contain normal excipients and no critical excipients are included. Therefore, the criteria for a BCS-based waiver has been fulfilled for Paracetamol/Codeïne Eurogenerics 500 mg/30 mg tablets.

### IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Paracetamol/Codeïne Eurogenerics. At the time of approval, the most recent version of the RMP was version 0.2 dated 23 July 2023.

**Table 1. Summary table of safety concerns as approved in RMP**

Important identified risks	Misuse, abuse and dependence (codeine)
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Dafalgan Codeïne. No new clinical studies were conducted. The MAH demonstrated through a biowaiver that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The package leaflet (PL) 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 PL was English.

The test consisted of a pilot test with three participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL 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.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paracetamol/Codeïne Eurogenerics 500 mg/30 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Dafalgan Codeine 500 mg/30 mg film-coated tablets. Dafalgan Codeine is a well-known medicinal product with an established favourable efficacy and safety profile.

No bioequivalence study has been performed, a biowaiver is claimed and can be granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Paracetamol/Codeïne Eurogenerics with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 February 2025.

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE -  
 SUMMARY**

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N.A.	-	-	-	-	-