COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol/Codeïnefosfaat Accord 500 mg/30 mg, effervescent tablet (paracetamol and codeine phosphate hemihydrate)

NL/H/5612/003/DC

Date: 24 March 2026

This module reflects the scientific discussion for the approval of Paracetamol/Codeïnefosfaat Accord 500 mg/30 mg, effervescent tablet. The procedure was finalised on 23 January 2024. 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
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/Codeïnefosfaat Accord 500 mg/30 mg, effervescent tablet, from Accord Healthcare B.V.

The product is indicated:

- in adult patients (18 years of age and older) for relief of severe pain.
- in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

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), Solpadol 500 mg/30 mg Effervescent Tablet, which has been registered by Sanofi-aventis Ireland Ltd in Ireland since 1991 via a national procedure (Irish Licence number PA23180/012/002).

The concerned member states (CMS) involved in this procedure were Finland, France, Ireland, Italy, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol/Codeïnefosfaat Accord is an effervescent tablet. The tablets are white to off-white, round, flat and bevelled edged, plain on both sides. Each tablet contains as active substances 500 mg of paracetamol and 30 mg of codeine phosphate hemihydrate equivalent to 22.1 mg of codeine.

The excipients are: citric acid (E 330), sorbitol (E420), sodium hydrogen carbonate (E500 (II)), povidone (E1201), simethicone, sodium carbonate (E500 (I)), saccharin sodium (E954), polyethylene glycol (E1521) and lemon flavour (maize maltodextrin, acacia gum (gum arabic, E414), natural flavouring substances, flavouring preparations, flavouring substances and alpha-tocopherol (E307)).

The effervescent tablets are packed in paper/polyethylene (PE)/aluminium (Alu)/Surlyn (copolymer of ethylene and methacrylic acid) strips.

II.2 Drug Substance

The drug substances are paracetamol and codeine phosphate hemihydrate , which are both established active substances described in the European Pharmacopoeia (Ph.Eur.). Paracetamol is a white to almost white, crystalline powder, sparingly soluble in water, freely soluble in ethanol (96%) and very slightly soluble in methylene chloride. Codeine phosphate hemihydrate is a white or almost white, crystalline powder or are small colourless crystals, freely soluble in water and slightly soluble or very slightly soluble in ethanol (96%).

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

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

For both drug substances, specifications are considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional tests for particle size (paracetamol) and microbial purity. Batch analytical data demonstrating compliance with this specification have been provided for six batches (three per manufacturing site) for paracetamol and three batches of codeine phosphate hemihydrate.

Stability of drug substance

According to the CEP for paracetamol, the re-test period is 66 months in site I and five years in site II, when stored under the stated conditions. According to the CEP of codeine phosphate hemihydrate, the re-test period is 60 months 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 are explained. The choices of the packaging and manufacturing process are justified in relation to the innovator product. As the product is an effervescent tablet, no dissolution study is required. The pharmaceutical development of the product has

been adequately performed. The MAH has discussed the suitability of the effervescent tablet for use in children.
A bioequivalence (BE) study has been performed. Adequate information about the test and reference product batches used has been provided. The suitability of the test product batch used in the BE study has been established.

Manufacturing process
Sufficient details are provided concerning the manufacturing process description and the in-process controls. The manufacturing process has been adequately validated although deviation from the requirements stated in European/ICH guidelines. Process validation data on the product have been presented for two commercial scale batches of the to be registered strength (500 mg/30 mg). In addition, validation data have been provided of two not to be registered strengths (500 mg/8 mg and 500 mg/15 mg). This is acceptable.

Control of excipients
The excipients comply with Ph. Eur. requirements where applicable, or with other relevant compendial requirements. 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, average weight, hardness, disintegration time, pH and clarity of solution, loss on drying, identity and assay of the active substances, uniformity of dosage units by content uniformity, related substances and microbial examination. The in-house methods for identity, assay and related substances and the methods for microbial quality have been adequately validated and are suitable for their intended use. The HPLC methods are stability-indicating, as shown by forced degradation studies. 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 three commercial scale batches, including the batch used in the BE study, from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for production scaled batches at 25°C/ 60% RH (3 batches for 36 months, one batch 3 months), 30°C/65% RH (3 batches, 12 months) and 40°C/75% RH (3 batches, 6 months). The stability was tested in accordance with ICH guidelines. A photostability study has been performed, demonstrating that the product is stable under light exposure. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are “Store below 25°C. Store in the original package in order to protect from moisture.”

As the SmPC states that the reconstituted solution is to be drunk immediately, no in-use stability study after reconstitution has been performed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Paracetamol/Codeïnefosfaat Accord 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 Solpadol 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 both 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, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Paracetamol/Codeïnefosfaat Accord 500 mg/30 mg, effervescent tablet (Accord Healthcare B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Solpadol 500 mg/30 mg Effervescent Tablet (Sanofi-aventis Ireland Ltd, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 37 healthy subjects (20 males and 20 females), aged 23-65 years. Each subject received a single dose (500 mg/30 mg) of one of the two paracetamol/codeine phosphate hemihydrate formulations. The tablet was orally administered with 240 ml water (by consuming the tablet dissolved in 120 ml water, followed by 120 ml plain water) after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of at least three days.

Blood samples were collected pre-dose and at 0.08, 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 7, 9, 12, 15, 18 and 24 hours after administration of the products.

The design of the study is acceptable.

Paracetamol and codeine phosphate hemihydrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of paracetamol and codeine phosphate hemihydrate . Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

40 Subjects enrolled in the study. Two subjects were withdrawn after dosing in Period I due to multiple adverse events (syncope, somnolence, nausea, vomiting, bradycardia, dyspnea and hypotension), one subject withdrew consent prior to Period II due to personal reasons. In total 37 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of paracetamol (upper side) and codeine phosphate hemihydrate (lower side), 500 mg/30 mg under fasted conditions.

Treatment N=37	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Paracetamol				
Test	25155 ± 6016	25717 ± 6311	10702 ± 3210	0.33 (0.17 - 0.83)
Reference	25214 ± 6662	25746 ± 6864	10346 ± 3018	0.25 (0.17 - 1.00)
***Ratio (90% CI)**	1.01 (0.99 - 1.03)	--	1.04 (0.97 - 1.11)	--
Codeine				
Test	285 ± 78	290 ± 79	108 ± 40	0.50 (0.33 - 1.27)
Reference	295 ± 93	300 ± 95	110 ± 42	0.50 (0.25 - 1.00)
***Ratio (90% CI)**	0.98 (0.94 – 1.02)	--	1.00 (0.90 – 1.11)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**In-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Paracetamol/Codeïnefosfaat Accord is considered bioequivalent with Solpadol.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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/Codeïnefosfaat Accord. At the time of approval, the most recent version of the RMP was version 1.2 with date of final sign off 22 November 2023.

Table 2. 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 Solpadol. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Solpadol 500 mg/30 mg mg Effervescent Tablet for the content and to Mycophenolic acid 180mg and 360mg gastro-resistant Tablets (ES/H/0183/001-002/DC) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paracetamol/Codeïnefosfaat Accord 500 mg/30 mg, effervescent tablet has a proven chemical-pharmaceutical quality and is a generic form of Solpadol 30 mg/500 mg Effervescent Tablet. Solpadol is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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/Codeïnefosfaat Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 January 2024.

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
NL/H/5612/003 /IA/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation: Change(s) in the Summary of product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a PRAC signal recommendation: implementation of wording agreed by the competent authority that do not require any further assessment	Yes	24-2-2025	Approved	N.A.
NL/H/5612/003 /IA/002	Change in the name and/or address of the marketing authorisation holder	Yes	27-5-2025	Approved	N.A