COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol/codeïnefosfaat/coffeïne Accord 500 mg/8 mg/30 mg effervescent tablets

(paracetamol, codeine phosphate hemihydrate and caffeine)

NL/H/5613/001/DC

Date: 6 March 2026

This module reflects the scientific discussion for the approval of Paracetamol/codeïnefosfaat/coffeïne Accord 500 mg/8 mg/30 mg effervescent tablets. The procedure was finalised on 2 November 2023. 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/coffeïne Accord 500 mg/8 mg/30 mg effervescent tablets, from Accord Healthcare B.V.

The product is indicated in patients 18 years of age and older for the short-term treatment of acute moderate pain which is not relieved by 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), Solpadeine Soluble Tablets 500/8/30 mg, which has been registered by Chefaro Ireland DAC in Ireland since 1978 (Irish Licence number PA1186/011/001).

The concerned member states (CMS) involved in this procedure were Ireland and Slovakia.

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol/codeïnefosfaat/coffeïne Accord is an effervescent tablet. The tablets are white to off-white, round and bevelled edged. Each tablet contains as active substances 500 mg of paracetamol, 5.9 mg of codeine (as 8 mg of codeine phosphate hemihydrate) and 30 mg of caffeine.

The excipients are: citric acid (E330), sorbitol (E420), sodium hydrogen carbonate (E500 (II)), povidone (E1201), simeticone, anhydrous sodium carbonate (E500 (I)), saccharin sodium (E954) and macrogol (E1521).

The effervescent tablets are packed in paper/polyethylene (PE)/aluminium (Alu)/ Surlyn (co-polymer of ethylene/methacrylic acid/zinc material) strips.

II.2 Drug Substance

The product contains three drug substances: paracetamol, codeine phosphate hemihydrate and caffeine, which are all established drug 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 small colourless crystals, freely soluble in water and slightly soluble or very slightly soluble in ethanol (96%).
Caffeine is a white to almost white, crystalline powder or are silky, white or almost white, crystals, sparingly soluble in water, freely soluble in boiling water and slightly soluble in ethanol (96%). It dissolves in concentrated solutions of alkali benzoates or salicylates.

The CEP procedure is used for all three drug 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 of the three drug substances have been included.

Quality control of drug substance
For all three drug substances, the specifications are considered adequate to control the quality and meet the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with these specifications have been provided for three batches of paracetamol from each supplier, three batches of codeine phosphate hemihydrate and three batches of caffeine.
Only the codeine phosphate hemihydrate CEP contains an additional test, for residual solvents.

Stability of drug substance
The re-test period of paracetamol is five years respectively 66 months, depending on the manufacturing site, when stored under the stated conditions. For codeine phosphate hemihydrate and caffeine, the re-test period is both 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. As the product is an effervescent tablet, no dissolution study is required. The pharmaceutical development of the product was adequately performed. The MAH has discussed the suitability of the effervescent tablet and of the selected excipients for use in children and the palatability of the solution for paediatric use.
A bioequivalence (BE) study has been performed. Adequate information about the test and reference product batches used has been provided.
A risk assessment on elemental impurities has been provided, which is acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for four commercial scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. requirements where applicable, or with other relevant compendial requirements. All relevant functionality-related characteristics are included in the specifications for the excipients. 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, uniformity of weight, average weight, hardness, disintegration time, pH and clarity of solution, loss on drying, identity and assay of the three active substances, uniformity of dosage units by content uniformity, related substances and microbial examination. The in-house methods for identification, 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. Appropriate tests for nitrosamine presence are performed on the final product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided on four commercial scale batches, including the batch used in the BE study, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months), and stability data at intermediate conditions 30°C/65% RH (12 months) have been provided for two batches. The stability was tested in accordance with applicable European guidelines. A photostability study has been provided, showing that the product is not sensitive to light. On basis of the data submitted, a

shelf life was granted of 3 years. The labelled storage conditions are 'Do not s*tore above 25°C. Store in the original packaging 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/coffeïne 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/coffeïne 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 Solpadeine 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, codeine phosphate hemihydrate and caffeine 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, besides 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/coffeïne Accord 500 mg/8 mg/30 mg effervescent tablets (Accord Healthcare B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Solpadeine Soluble Tablets, 500/8/30 mg (Chefaro Ireland DAC, Ireland).

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

Bioequivalence studies

Design

An open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy subjects (20 males and 20 females), aged 18-65 years. Each subject received a single dose (500 mg/8 mg/30 mg) of one of the two paracetamol/ codeine phosphate hemihydrate/ caffeine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of three days.

Blood samples were collected pre-dose and at 0.08, 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 7, 9, 12, 15, 18 and 24 hours after administration of the products.

The design of the study is acceptable.

Paracetamol, codeine phosphate hemihydrate and caffeine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of paracetamol, codeine phosphate hemihydrate and caffeine. 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. One subject withdrew consent prior to period II, for personal reasons. In total, 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of paracetamol, 500 mg under fasted conditions.

Treatment N=38[1]	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	23788 ± 7044	24142 ± 7159	10529 ± 2727	0.25 (0.08 – 1.5)
Reference	23564 ± 6990	23927 ± 7077	9731 ± 2369	0.30 (0.17 – 0.83)
***Ratio (90% CI)**	1.01 (0.99 – 1.03)	--	1.08 (1.01 – 1.14)	--

$AUC_{0-\infty}$	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

**ln-transformed values*
[1] = One subject was excluded from the analysis due to a pre-dose concentration >5% of the C_{max} in both respective periods.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of codeine phosphate hemihydrate, 8 mg under fasted conditions.

Treatment N=39	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	74.7 ± 23.1	77.6 ± 23.0	27.7 ± 6.8	0.5 (0.25 – 1.75)
Reference	70.8 ± 21.9	73.8 ± 22.1	26.1 ± 7.9	0.5 (0.33 – 0.83)
***Ratio (90% CI)**	1.06 (1.02 – 1.10)	--	1.07 (1.00 – 1.16)	--

$AUC_{0-\infty}$	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

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of caffeine, 30 mg under fasted conditions.

Treatment N=31[2]	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	5592 ± 1626	6001 ± 1818	1031 ± 256	0.25 (0.17 – 1.5)
Reference	5700 ± 1839	6276 ± 2200	983 ± 232	0.30 (0.17 – 0.83)
***Ratio (90% CI)**	0.99 (0.95 – 1.02)	--	1.04 (0.99 – 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

**ln-transformed values*

[2] = Eight subjects were excluded from the analysis due to a pre-dose concentration >5% of the C_{max} in one or both respective periods.

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 for each of the three drug substances. Based on the submitted bioequivalence study Paracetamol/codeïnefosfaat/coffeïne Accord is considered bioequivalent with Solpadeine.

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/coffeïne Accord. At the time of approval, the most recent version of the RMP was version 1.3 with date of final sign-off 19 October 2023.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	Misuse, abuse, 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 Solpadeine. 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

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.

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 Solpadeine Soluble Tablets 500/8/30 mg, (Irish Licence number PA1186/011/001) for the content and to Mycophenolic Acid Accord 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC) for design, layout and style of writing. 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/coffeïne Accord 500 mg/8 mg/30 mg effervescent tablets have a proven chemical-pharmaceutical quality and are generic forms of Solpadeine Soluble Tablets 500/8/30 mg. Solpadeine 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/coffeïne Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 November 2023.

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/5613/001 /IB/001	Change(s) to therapeutic indication(s) - Deletion of a therapeutic indication	Yes	7-4-2025	Approved	N.A.
NL/H/5613/001 /IA/002	Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	No	9-1-2025	Approved	N.A.
NL/H/5613/001 /IA/003	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 does not require any further assessment. Update sections 4.4, 4.5, 4.8 of the SmPC and sections 2, 4 of the leaflet to implement the signal	Yes	24-2-2025	Approved	N.A.

	recommendations on Paracetamol (single ingredient and fixed dose combinations) – High anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis (EPITT no 20105) adopted at the 28-31 October 2024 PRAC meeting.				