



Medicines & Healthcare products
Regulatory Agency



Public Assessment Report

UKPAR

**Co-Codamol 30/500mg Effervescent Tablets
(codeine phosphate hemihydrate and paracetamol)**

UK Licence No: PL 31603/0020

Apollo Generics Limited

LAY SUMMARY

Co-Codamol 30/500mg Effervescent Tablets (codeine phosphate hemihydrate and paracetamol)

This is a summary of the Public Assessment Report (PAR) for Co-Codamol 30/500mg Effervescent Tablets (PL 31603/0020). It explains how the application for Co-Codamol 30/500mg Effervescent Tablets (PL 31603/0020) was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Co-Codamol 30/500mg Effervescent Tablets (PL 31603/0020). For ease of reading, this product will be referred to as 'Co-Codamol Effervescent Tablets' in this lay summary.

For practical information about using Co-Codamol Effervescent Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Co-Codamol Effervescent Tablets and what are they used for?

Co-Codamol Effervescent Tablets are a 'generic' medicine'. This means that Co-Codamol Effervescent Tablets are similar to a 'reference medicine' already authorised in the UK called Solpadol 30mg/500mg Effervescent Tablets (PL 04425/0636; Aventis Pharma Limited).

Co-Codamol Effervescent Tablets are used to treat severe pain.

Co-Codamol Effervescent Tablets can be used in children over 12 years of age for the short-term relief of moderate pain that is not relieved by other painkillers such as paracetamol or ibuprofen alone.

How do Co-Codamol Effervescent Tablets work?

Co-Codamol Effervescent Tablets contain two different analgesic medicines called codeine phosphate hemihydrate and paracetamol. Codeine belongs to a group of medicines called opioid analgesics which act to relieve pain.

How are Co-Codamol Effervescent Tablets used?

This medicine can only be obtained with a prescription.

The pharmaceutical form of this medicine is an effervescent tablet and the tablets are taken by mouth after being dissolved in water.

The patient should always take Co-Codamol Effervescent Tablets exactly as his/her doctor or pharmacist has advised. The patient should check with his/her doctor or pharmacist if unsure.

The tablet(s) should be dissolved in at least half a glass of water before swallowing the contents of the glass.

Children aged under 12 years

Co-codamol should not be given to children below the age of 12 years, due to the risk of severe breathing problems.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

What benefits of Co-Codamol Effervescent Tablets have been shown in studies?

The company provided data from studies to determine that Co-Codamol Effervescent Tablets are bioequivalent to the reference medicine Solpadol 30mg/500mg Effervescent Tablets (PL 04425/0636; Aventis Pharma Limited). Two medicines are bioequivalent when they produce the same levels of the active substance(s) in the body.

What are the possible side effects of Co-Codamol Effervescent Tablets?

Because Co-Codamol Effervescent Tablets are a generic medicine and as they are considered to be bioequivalent to the reference medicine Solpadol 30mg/500mg Effervescent Tablets (PL 04425/0636; Aventis Pharma Limited), their benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Co-Codamol Effervescent Tablets, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet available on the MHRA website.

Why are Co-Codamol Effervescent Tablets approved?

It was concluded that, in accordance with EU requirements, Co-Codamol Effervescent Tablets have been shown to have comparable quality and to be bioequivalent to Solpadol 30mg/500mg Effervescent Tablets (PL 04425/0636; Aventis Pharma Limited). Therefore, the MHRA decided that, as for Solpadol 30mg/500mg Effervescent Tablets (PL 04425/0636; Aventis Pharma Limited), the benefits are greater than the risks and recommended that Co-Codamol Effervescent Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Co-Codamol Effervescent Tablets?

A Risk Management Plan (RMP) has been developed to ensure that Co-Codamol Effervescent Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Co-Codamol Effervescent Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Co-Codamol Effervescent Tablets

A Marketing Authorisation for Co-Codamol Effervescent Tablets (PL 31603/0020) was granted in the UK to Apollo Generics Limited on 13 September 2018.

The full PAR for Co-Codamol Effervescent Tablets follows this summary.

For more information about use of Co-Codamol Effervescent Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2018.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

| | | |
|-----|--|---------|
| I | Introduction | Page 5 |
| II | Quality aspects | Page 5 |
| III | Non-clinical aspects | Page 7 |
| IV | Clinical aspects | Page 8 |
| V | User consultation | Page 10 |
| VI | Overall conclusion, benefit/risk assessment and recommendation | Page 10 |
| | Steps taken after the initial procedure - Summary | Page 15 |

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for Co-Codamol 30/500mg Effervescent Tablets (PL 31603/0020) to Apollo Generics Limited on 13 September 2018. For ease of reading, the product may be referred to as 'Co-Codamol Effervescent Tablets' in this scientific discussion.

The product is a Prescription Only Medicine (POM) indicated for the relief of severe pain. Co-Codamol Effervescent Tablets are also indicated 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).

The application for Co-Codamol 30/500mg Effervescent Tablets was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference medicinal product Solpadol 30mg/500mg Effervescent Tablets (PL 04425/0636; Aventis Pharma Limited), which was granted on 27 January 2009 following a series of Change of Ownership procedures of Paracetamol 500mg and Codeine Phosphate 30mg Effervescent Tablets (PL 00071/0332; SmithKline Beecham Limited), which was granted on 19 December 1989.

Co-codamol Effervescent Tablets contain the active ingredients codeine phosphate hemihydrate and paracetamol, which are both analgesics (painkillers).

The exact mechanism of action of paracetamol is not completely understood; it is supposed to be mediated peripherally and within the central nervous system. Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

No new non-clinical data were submitted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for this application. A suitable justification for a Biopharmaceutics Classification System (BCS) - based biowaiver has been provided for this application.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Co-Codamol Effervescent Tablets outweigh the risks, and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a white round, biplane, single scored effervescent tablet. The score line is not intended for breaking the tablet.

Each effervescent tablet contains 30 mg codeine phosphate hemihydrate and 500 mg of paracetamol, as the active substances. The product also contains pharmaceutical excipients namely, sodium hydrogen carbonate, povidone (K29-32), citric acid anhydrous, sorbitol, lactose monohydrate, saccharin

sodium, lemon flavour, ascorbic acid and L-leucine. Appropriate justification for the inclusion of each excipient has been provided.

Co-codamol Effervescent Tablets are packaged in polypropylene tubes containing either 16 or 20 effervescent tablets packed into cardboard cartons. The product is available in pack sizes of 16, 20, 32, 40, 48 and 60 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

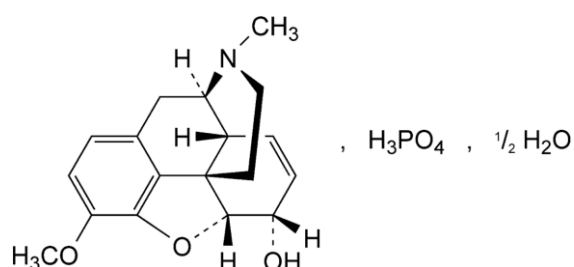
II.2 DRUG SUBSTANCE

Codeine phosphate hemihydrate

INN: Codeine phosphate hemihydrate

Chemical name: 4,5 α -Epoxy-3-methoxy-17-methyl-7,8-didehydromorphinan-6 α -ol phosphate hemihydrate

Structure:



Molecular formula: C₁₈H₂₄NO₇P·1/2H₂O

Mr: 406.4

Appearance: A white or almost white, crystalline powder or small colourless crystals

Solubility: Freely soluble in water, slightly soluble or very slightly soluble in ethanol (96 per cent).

Codeine phosphate hemihydrate is the subject of a European Pharmacopoeia monograph.

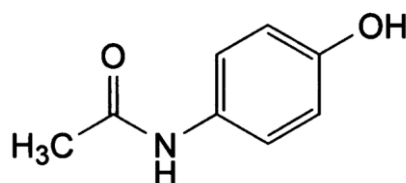
All aspects of the manufacture and control of the active substance, codeine phosphate hemihydrate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Paracetamol

INN: Paracetamol

Chemical name: N-(4-hydroxyphenyl)acetamide

Structure:



Molecular formula: C₈H₉NO₂

Mr: 151.2

Appearance: White or almost white crystalline powder

Solubility: Paracetamol is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride

Paracetamol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, paracetamol, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable effervescent tablets, each containing 30 mg of codeine phosphate hemihydrate and 500 mg of paracetamol, that could be considered bioequivalent to the reference product Solpadol 30mg/500mg Effervescent Tablets (PL 04425/0636; Aventis Pharma Limited). Suitable pharmaceutical development data have been provided to support this application.

With the exception of lemon flavour, which is controlled to a suitable in-house specification, all excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 3 years, with the special storage conditions, 'Do not store above 30 °C. Store this product in its original package to protect from moisture and light. Keep the container tightly closed.' has been approved.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence

A bioequivalence study was not necessary to support this application. A suitable justification for a BCS - based biowaiver has been submitted for this application.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application, from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of codeine phosphate hemihydrate and paracetamol are well-known, no new non-clinical studies are required, and none have been provided.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology for codeine phosphate hemihydrate and paracetamol.

III.2 Pharmacology

No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics

No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

III.4 Toxicology

No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for substitution of an already authorised product, it is not expected that environmental exposure of codeine phosphate hemihydrate and paracetamol will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

There are no objections to the approval of this application, from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of codeine phosphate hemihydrate and paracetamol is well-known. No new clinical pharmacokinetic data are provided or required for this application.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

The applicant has not submitted a bioequivalence study to support these applications and none was required as the product meets the criteria regarding oral solutions specified in the guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). The test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an oral solution of the reference product. The excipients are not expected to affect the gastrointestinal transit, absorption or *in vivo* stability of the active substance. The justification for a BCS biowaiver can be accepted.

IV.2 Pharmacokinetics

The pharmacokinetic profiles of codeine phosphate hemihydrate and paracetamol are well known. No new clinical pharmacokinetic data are provided or required for this application.

The justification for BCS - based biowaiver can be accepted.

IV.3 Pharmacodynamics

The clinical pharmacodynamic properties of codeine phosphate hemihydrate and paracetamol are well-known. No new pharmacodynamic data were submitted and none were required for this type of application.

IV.4 Clinical efficacy

No new efficacy data were submitted, and none were required for this type of application.

IV.5 Clinical safety

No new safety data were submitted, and none are required for this type of application. The safety profiles of codeine phosphate hemihydrate and paracetamol are well-known. No new or unexpected safety issues arose from this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Marketing Authorisation Holder (MAH) has submitted a Risk Management Plan (RMP), 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 Co-codamol Effervescent Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Table 1: Summary table of safety concerns

| Summary of safety concerns | |
|----------------------------|--|
| Important identified risks | <ul style="list-style-type: none"> • Hypersensitivity – including serious skin reactions • Use in patients with respiratory depression • Use in patients with acute asthma and obstructive airway disease • Use in patients with head injuries and raised intracranial pressure • Use in patients after biliary surgery • Use in patients with acute abdominal conditions (including diarrhoea) • Use in patients with hypothyroidism • Use in patients with Addison's disease • Use in patients with prostatic hypertrophy • Use in patients with urethral stricture • Use in patients who have received monoamine oxidase inhibitors within the previous 14 days • Addiction and drug dependence • Overdose – intentional and unintentional • Hepatic toxicity when used in combination with other paracetamol products, in those with non-cirrhotic alcoholic liver disease, or combined with alcohol • Increased risk of serious and life threatening adverse reactions including death in paediatric patients who undergo tonsillectomy and/or adenoidectomy • Opioid toxicity in children less than 12 years of age • Bleeding – interactions with warfarin and coumarins • Patients with renal impairment • Use in patients with fructose intolerance • Use in patients on controlled sodium diet |
| Important potential risks | <ul style="list-style-type: none"> • Use in elderly and debilitated patients • Use during pregnancy and lactation • Driving and using machines |
| Missing information | None |

Routine pharmacovigilance and routine risk minimisation activities are acceptable to monitor the safety concerns described in the Risk Management Plan.

IV.7 Discussion on the clinical aspects

The justification for a BCS - based biowaiver for Co-Codamol Effervescent Tablets is accepted.

The grant of a Marketing Authorisation is recommended for this application, from a clinical point of view.

V USER CONSULTATION

The submitted PIL text is satisfactory. The Marketing Authorisation Holder (MAH) has committed to submitting mock-up livery and a full user test, to the relevant regulatory authorities, for approval before packs are marketed.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with codeine phosphate hemihydrate and paracetamol is considered to have demonstrated the therapeutic value of the compounds. A suitable justification for a BCS - based biowaiver has been accepted.

The benefit/risk assessment is, therefore, considered to be positive.

The grant of a Marketing Authorisation is recommended.

The SmPC, PIL and labelling text are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-ups to the regulatory authorities for approval before packs are marketed. The current labelling text is presented below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

{Carton}

1. NAME OF THE MEDICINAL PRODUCT

Co-Codamol 30/500mg Effervescent Tablets
Codeine Phosphate Hemihydrate and Paracetamol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each effervescent tablet contains 30mg codeine phosphate hemihydrate and 500mg paracetamol

3. LIST OF EXCIPIENTS

Sodium content 316mg per tablet. Also contains sorbitol and lactose. See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Effervescent tablets

16 tablets
20 tablets
32 tablets
40 tablets
48 tablets
60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. The tablets must be dissolved in water before taking.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not exceed the stated dose

Contains paracetamol

Do not take anything else containing paracetamol while taking this medicine

Talk to a doctor at once if you take too much of this medicine, even if you feel well

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor

Do not take for longer than directed by your prescriber as taking codeine regularly for a long time can lead to addiction.

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C. Store this product in its original package to protect from moisture and light.
Keep the container tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

N/A

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Apollo Generics Limited
Unit 1, 76 Stephenson Way
Formby Business Park
Liverpool
Merseyside
L37 8EG
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 31603/0020

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

N/A

16. INFORMATION IN BRAILLE

Co-Codamol 30/500mg Effervescent Tablets

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING
{TUBE}****1. NAME OF THE MEDICINAL PRODUCT**

Co-Codamol 30/500mg Effervescent Tablets
Codeine phosphate hemihydrate 30mg
Paracetamol 500mg
Tablets

2. METHOD OF ADMINISTRATION

The tablets must be dissolved in water before taking.

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

Read the package leaflet before use.

3. EXPIRY DATE

EXP (MM/YYYY)

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

16 Effervescent Tablets
20 Effervescent Tablets

6. OTHER

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not exceed the stated dose

Contains Paracetamol.

Do not take anything else containing paracetamol while taking this medicine.

Talk to a doctor at once if you take too much of this medicine, even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

Contains sodium 316mg, Sorbitol and Lactose

**Co-Codamol 30/500mg Effervescent Tablets
(codeine phosphate hemihydrate and paracetamol)**

PL 31603/0020

STEPS TAKEN AFTER THE INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|-----------------------|-------------------------|--------------|----------------|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |