Public Assessment Report

UKPAR

Co-codamol 15/500mg Tablets

(codeine phosphate hemihydrate and paracetamol)

UK Licence No: PL 29831/0588

Wockhardt UK Ltd
LAY SUMMARY
Co-codamol 15/500mg Tablets
(codeine phosphate hemihydrate and paracetamol)

This is a summary of the Public Assessment Report (PAR) for Co-codamol 15/500mg Tablets (PL 29831/0588). It explains how Co-codamol 15/500mg Tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Co-codamol 15/500mg Tablets.

For practical information about using Co-codamol 15/500mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Co-codamol 15/500mg Tablets and what are they used for?
Co-codamol 15/500mg Tablets are a medicine with ‘well established use’. This means that the medicinal use of the active substances, codeine phosphate hemihydrate and paracetamol, is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

This medicine is used to relieve moderate pain.

How do Co-codamol 15/500mg Tablets work?
Co-codamol 15mg/500mg Tablets contain the active substances codeine phosphate hemihydrate and paracetamol. Codeine phosphate hemihydrate belongs to a group of medicines called opioid analgesics which act to relieve pain. Paracetamol is also an antipyretic which means that it helps to reduce fever and lower the temperature.

Codeine phosphate hemihydrate and paracetamol are used for the treatment of acute moderate pain which is not relieved by other analgesics such as paracetamol or ibuprofen alone.

How are Co-codamol 15/500mg Tablets used?
The pharmaceutical form of this medicinal product is a tablet and should be taken orally (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose for adults is 2 tablets every 4 hours when necessary up to a maximum of 8 tablets in 24 hours. Elderly people may be prescribed a lower dose.

Use in children and adolescents
The recommended dose for children aged 16-18 years is 1-2 tablets every 6 hours when necessary up to a maximum of 8 tablets in 24 hours.

The recommended dose for children aged 12 to 15 years is 1 tablet every 6 hours when necessary up to a maximum of 4 tablets in 24 hours. Co-codamol 15/500mg Tablets should not be taken by children below the age of 12 years, due to the risk of severe breathing problems.

This medicine should not be taken for more than 3 days. If the pain does not improve after 3 days, the patient must talk to a doctor for advice. The patient must not take more than 4 doses in any 24 hours.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.
This medicine can only be obtained with a prescription.

**What benefits of Co-codamol 15/500mg Tablets have been shown in studies?**
As codeine phosphate hemihydrate and paracetamol are well-known substances, and their use in the licensed indications is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the use of codeine phosphate hemihydrate and paracetamol in the licensed indications.

**What are the possible side effects of Co-codamol 15/500mg Tablets?**
Like all medicines, Co-codamol 15/500mg Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Co-codamol 15/500mg Tablets, see section 4 of the package leaflet available on the MHRA website.

Also, for the full list of restrictions, see the package leaflet.

**Why were Co-codamol 15/500mg Tablets approved?**
The MHRA concluded that, in accordance with EU requirements, the benefits of Co-codamol 15/500mg Tablets outweigh the identified risks and recommended that the product be approved for use.

**What measures are being taken to ensure the safe and effective use of Co-codamol 15/500mg Tablets?**
A risk management plan (RMP) has been developed to ensure that Co-codamol 15/500mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Co-codamol 15/500mg 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 15/500mg Tablets**
The Marketing Authorisation for Co-codamol 15/500mg Tablets was granted in the UK on 03 January 2019.

The full PAR for Co-codamol 15mg/500mg Tablets follows this summary.

This summary was last updated in February 2019.
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th></th>
<th>Introduction</th>
<th>Page 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 6</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 8</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 8</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 12</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and</td>
<td>Page 12</td>
</tr>
<tr>
<td></td>
<td>recommendation</td>
<td></td>
</tr>
</tbody>
</table>

Table of content of the PAR update                  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 Wockhardt UK Ltd a Marketing Authorisation for the medicinal product Co-codamol 15/500mg Tablets (PL 29831/0588) on 03 January 2019.

The product is a prescription only medicine (POM), indicated for the relief of moderate pain. Codeine is 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).

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

Co-codamol 15/500mg Tablets contain the active substances codeine phosphate hemihydrate and paracetamol. Paracetamol has analgesic and antipyretic effects that do not differ significantly from those of aspirin. Its anti-inflammatory action is weak, and it has practically no anti-platelet effect. The mechanism of action is unclear, although it is believed to exert its action by inhibition of prostaglandin synthesis.

Codeine is a centrally acting weak analgesic. Codeine exerts its effects 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.

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.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application, and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Co-codamol 15/500mg Tablets outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 15 mg of codeine phosphate hemihydrate and 500 mg of paracetamol, as active substances. Other ingredients consist of the pharmaceutical excipients pregelatinised starch, povidone and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

None of the excipients contain material of animal or human origin. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

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

The finished product is packaged in polyvinylchloride (PVC)/glassine/aluminium child resistant foil blister packs and is available in pack sizes of 30, 90 or 100 tablets.

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

II.2 Drug Substances

1) Codeine phosphate hemihydrate

INN: Codeine phosphate hemihydrate
Chemical name: 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate hemihydrate.
Structure:

Molecular formula: \( \text{C}_{18}\text{H}_{24}\text{NO}_{7}\text{P} \cdot \frac{1}{2}\text{H}_{2}\text{O} \)
Molecular weight: 406.4 g/mol
Appearance: 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.

2) Paracetamol

INN: Paracetamol
Chemical name: \( \text{N-(4-Hydroxyphenyl)acetamide.} \)

Structure:

\[
\begin{align*}
\text{O} & \quad \text{H}_2\text{C} \\
\text{N} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\text{H} & \quad \text{C} \\
\text{OH} & \quad \text{O} \\
\end{align*}
\]

Molecular formula: \( \text{C}_8\text{H}_9\text{NO}_2 \)
Molecular weight: \( 151.2 \text{ g/mol} \)
Appearance: White or almost white, crystalline powder.
Solubility: Sparingly soluble in water, freely soluble in alcohol, 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, tablet containing 15 mg of codeine phosphate hemihydrate and 500 mg of paracetamol per tablet.

Comparative dissolution profiles have been presented for the test and the existing products.

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 and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf life of 3 years with storage conditions “Store below 25°C” and “Store in the original package” have been set. These are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.
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. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology data.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since this medicine is intended for substitution with other Co-codamol products that are currently marketed, no increase in environmental exposure to codeine phosphate hemihydrate and paracetamol is expected when this product is introduced to the market. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

CLINICAL ASPECTS

IV.1 Introduction
Codeine phosphate hemihydrate and paracetamol are well-established active substances. The details of the pharmacokinetics of the two active substances are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. The applicant did not conduct any new research or provide any new data. This is acceptable.

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

IV.2 BIOWAIVER
A biowaver was accepted as both phosphate hemihydrate and paracetamol are Biopharmaceutics Classification System (BCS) Class I substances and, as such, bioequivalence is not required.

IV.3 Pharmacokinetics
The pharmacokinetics of codeine phosphate hemihydrate and paracetamol have been thoroughly reviewed in the clinical overview, and the summary of product characteristics (SmPC) adequately reflects the known pharmacokinetic properties of paracetamol/codeine.

IV.4 Pharmacodynamics
The well-established pharmacodynamic profile for this analgesic combination has been reviewed in the clinical overview. No new studies have been conducted and none are required for this type of application.
IV.5  Clinical efficacy
The well-established efficacy profile for this analgesic combination has been reviewed in the clinical overview. No new studies have been conducted and none are required for this type of application.

IV.6  Clinical safety
The well-established safety profile of this analgesic combination has been reviewed in the clinical overview. Both classes of drugs have different mechanisms of action and very different side effect profiles. There are no new concerns and relevant sections of the SmPC are consistent with those of similar approved products and adequately cover the safety profile.

IV.7  Risk Management Plan (RMP)
The Marketing Authorisation Holder 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 Co-codamol 15/500mg Tablets.

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

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Use in patients with medication overuse headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective(s) of the risk minimisation measures</td>
<td>To provide adequate information and warnings to prescribers and patients</td>
</tr>
<tr>
<td>Routine risk minimisation measures</td>
<td>Routine risk minimisation</td>
</tr>
<tr>
<td></td>
<td>The SmPC is up to date. Section 4.2 states “Do not take for more than 3 days without consulting your doctor…”</td>
</tr>
<tr>
<td></td>
<td>Other routine risk minimisation measures</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine</td>
</tr>
<tr>
<td>Additional risk minimisation measure(s) (repeat as necessary)</td>
<td>none</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Effectiveness of risk minimisation measures</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>How effectiveness of risk minimisation measures for the safety concern will be measured</td>
<td>In accordance with routine pharmacovigilance activities.</td>
</tr>
<tr>
<td>Criteria for judging the success of the proposed risk minimisation measures</td>
<td>In accordance with routine pharmacovigilance activities.</td>
</tr>
<tr>
<td>Planned dates for assessment</td>
<td>In accordance with routine pharmacovigilance activities.</td>
</tr>
<tr>
<td>Results of effectiveness measurement</td>
<td>Results are not yet available.</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Overdose</td>
</tr>
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<td>---------------</td>
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</tr>
<tr>
<td>Objective(s) of the risk minimisation measures</td>
<td>To provide adequate information and warnings to prescribers and patients</td>
</tr>
<tr>
<td>Routine risk minimisation measures</td>
<td>Routine risk minimisation</td>
</tr>
<tr>
<td></td>
<td>The SmPC is up to date.</td>
</tr>
<tr>
<td></td>
<td><strong>Section 4.4 Special warnings and precautions for use:</strong></td>
</tr>
<tr>
<td></td>
<td>The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.</td>
</tr>
<tr>
<td></td>
<td>Patients should be advised that immediate medical advice should be sought in the event of an overdose, because of the risk of delayed, serious liver damage. They should be advised not to take other paracetamol-containing products concurrently and to keep the product out of the reach of children.</td>
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<tr>
<td></td>
<td><strong>Section 4.9 Overdose</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td></td>
<td>Symptoms of paracetamol overdose in the first 24 hours are sweating, pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, hypotension, cerebral oedema, coma and death. Prothrombin time may increase with deteriorating liver function. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported. Liver damage is possible in adults who have taken 10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.</td>
</tr>
<tr>
<td></td>
<td>An overdose with codeine is characterised by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdose with codeine, apnoea, circulatory collapse, cardiac arrest and death may occur.</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Overdose</td>
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<td>---------------</td>
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</tr>
<tr>
<td></td>
<td>Treatment</td>
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<td></td>
<td>Paracetamol: Immediate treatment is essential in the management of paracetamol overdose. Despite lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any patient who has ingested around 7.5 g or more of paracetamol in the proceeding 4 hours should undergo gastric lavage. Administration of oral methionine or intravenous N-acetylcysteine which may have a beneficial effect up to at least 48 hours after the overdose, may be required. General supportive measures must be available.</td>
</tr>
<tr>
<td></td>
<td>Codeine: Primary attention should be given to the re-establishment of adequate respiratory function through the provision of a patent airway and the institution of controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Opioid antagonists, such as naloxone may be administered.</td>
</tr>
<tr>
<td></td>
<td>Other routine risk minimisation measures</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine</td>
</tr>
<tr>
<td>Additional risk minimisation measure(s) (repeat as necessary)</td>
<td>none</td>
</tr>
</tbody>
</table>

**Effectiveness of risk minimisation measures**

| How effectiveness of risk minimisation measures for the safety concern will be measured | In accordance with routine pharmacovigilance activities. |
| Criteria for judging the success of the proposed risk minimisation measures | In accordance with routine pharmacovigilance activities. |
| Planned dates for assessment | In accordance with routine pharmacovigilance activities. |
| Results of effectiveness measurement | Results are not yet available. |
| Impact of risk minimisation | As no results regarding the effectiveness of risk minimisation are yet available, the impact of risk minimisation measures cannot be evaluated. |
Routine risk minimisation is provided through the summary of product characterisation and the patient information leaflet. No additional risk minimisation measures are planned for this product.

**Discussion on the clinical aspects**
The grant of a Marketing Authorisation is recommended for this application.

**V USER CONSULTATION**
User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Co-codamol 8/500mgTablets (PL 29831/0117). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

**VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with codeine phosphate hemihydrate and paracetamol is considered to have demonstrated the therapeutic value of the compounds. The benefit risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Co-codamol 15/500mg Tablets is presented below:
PAR Co-codamol 15/500mg Tablets
Table of content of the PAR update
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitment)

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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