Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

Co-dydramol 20/500 mg Tablets
PL 04077/0243

Co-dydramol 30/500 mg Tablets
PL 04077/0244

Dihydrocodeine hydrogen tartrate, paracetamol

M&A Pharmachem Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Co-dydramol 20/500 mg Tablets (PL 04077/0243) and Co-dydramol 30/500 mg Tablets (PL 04077/0244). Co-dydramol 20/500 mg Tablets and Co-dydramol 30/500 mg Tablets will be termed Co-dydramol Tablets throughout this Lay Summary for ease of reading. This PAR explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Co-dydramol Tablets, patients should read the Package Leaflet or contact their doctor or pharmacist.

What are Co-dydramol Tablets and what are they used for?
Co-dydramol Tablets are used to relieve severe pain.

How do Co-dydramol Tablets work?
These products contain either 20 mg dihydrocodeine hydrogen tartrate and 500 mg paracetamol, or 30mg dihydrocodeine hydrogen tartrate and 500 mg paracetamol. Both dihydrocodeine hydrogen tartrate and paracetamol are analgesics (painkillers).

How are Co-dydramol Tablets used?
These products are prescription only medicines (POM).

These medicines are for oral use. Tablets should be swallowed with a glass of water, preferably during or after a meal.

These medicines are not recommended for children under 12 years.

For adolescents aged between 12 and 15 years, one tablet should be taken every 4-6 hours. Do not take more than four tablets in any 24-hour period.

For adults aged 16 and over, one or two tablets should be taken every 4-6 hours. Do not take more than two tablets at once and do not take more than eight tablets in any 24-hour period.

For the elderly, one tablet should be taken every 4-6 hours, increasing to two tablets every 4-6 hours, if required and tolerated. Do not take more than eight tablets in a 24-hour period. Caution should be taken when increasing the dose in the elderly.

Please read Section 3 of the Package Leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

How have Co-dydramol Tablets been studied?
Because these products have been submitted as well-established use applications based on medicines that have been used for many years, no new studies in patients have been performed. Suitable data in the form of literature references have been provided to show the suitability of these products for the proposed indications.

What are the possible side effects of Co-dydramol Tablets?
Because these applications have been submitted as well-established use applications, the benefits of these medicines and possible side-effects are taken as being the same as other similar products that are already marketed.

For further information, please see Section 4 the Package Leaflet.

Why are Co-dydramol Tablets approved?
It was concluded that, based on the data submitted for these medicines, the benefits outweigh the identified risks and it was recommended that Co-dydramol Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Co-dydramol Tablets?
A risk management plan (RMP) has been developed to ensure that Co-dydramol 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-dydramol 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 and healthcare professionals will be monitored and reviewed continuously, as well.

Other information about Co-dydramol Tablets
Marketing authorisations were granted in the UK on 10 February 2017.

The full PAR for Co-dydramol Tablets follows this summary.

For more information about treatment with Co-dydramol Tablets, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in April 2017.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA considered that the applications for Co-dydramol 20/500 mg Tablets (PL 04077/0243) and Co-dydramol 30/500 mg Tablets (PL 04077/0244) could be approved.

Co-dydramol 20/500 and 30/500 mg Tablets are indicated for the treatment of severe pain. These medicines are not to be taken by children under 12 years old.

These products contain the active substances paracetamol and dihydrocodeine (as dihydrocodeine hydrogen tartrate).

Paracetamol [acetaminophen; N-(4-hydroxyphenyl) acetamide] is a para-aminophenol derivative with analgesic, antipyretic and weak anti-inflammatory properties. It is rapidly absorbed and its pharmacokinetics have been extensively studied.

Dihydrocodeine is an opioid analgesic drug, commonly used in combination with non-opioid analgesics in a number of proprietary preparations.

These applications were made under Article 10a of Directive 2001/83/EC, as amended, well-established use applications.

No new non-clinical studies were conducted, which is acceptable given that these are well-established use applications. Suitable non-clinical data have been submitted in the form of literature references.

Since these products contain active substances that are well established and have been used in the UK for decades, and these products are intended for substitution with products that are already marketed, no increased exposure of these products to the environment is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

No clinical studies were conducted, which is acceptable given that these are well-established use applications. Suitable clinical data have been submitted in the form of literature references.

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, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A satisfactory Risk Management Plan (RMP) and summary of the pharmacovigilance system have been provided with these applications.

National licences were granted in the UK on 10 February 2017.

II QUALITY ASPECTS

II.1 Introduction

These applications are submitted according to Article 10a of Directive 2001/83/EC, as amended, so-called well-established use applications.

Co-dydramol 20/500 mg Tablets contain 20 mg dihydrocodeine hydrogen tartrate and 500 mg paracetamol. Co-dydramol 30/500 mg Tablets contain 30 mg dihydrocodeine hydrogen tartrate and 500 mg paracetamol.

In addition to the above active substances, these products also contain the excipients maize starch, colloidal silica, potassium sorbate, povidone and magnesium stearate.

The finished products are tablets, packaged in child-resistant aluminium/polyvinylchloride blisters in pack sizes of 56 or 112 tablets. All packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCES

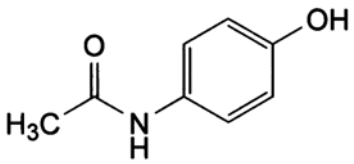
II.2.1 Paracetamol

rINN: Paracetamol

Formula: $C_8H_9NO_2$

MW: 151.17

Structure:



Chemical name: N-(4-hydroxyphenyl)acetamide

Description: White or almost white crystalline powder, sparingly soluble in water, freely soluble in alcohol and very slightly soluble in dichloromethane.

Paracetamol is the subject of a European Pharmacopoeial monograph.

All aspects of the manufacture and control of paracetamol are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) certificate of suitability.

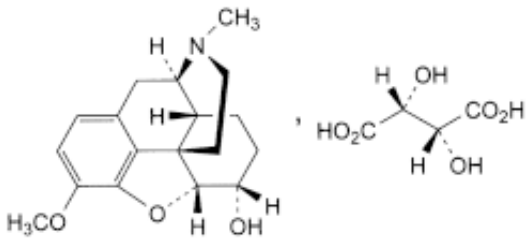
II.2.2 Dihydrocodeine hydrogen tartrate

rINN: Dihydrocodeine hydrogen tartrate

Formula: $C_{18}H_{23}NO_3.C_4H_6O_6$

Relative molecular mass: 451.5

Structure:



Chemical name: 4, 5 α-Epoxy-3-methoxy-17-methylmorphinan-6α-ol hydrogen (2R, 3R) -2, 3-dihydroxybutanedioate

Description: A white or almost white crystalline powder, freely soluble in water and sparingly soluble in alcohol.

Dihydrocodeine hydrogen tartrate is the subject of a European Pharmacopoeial monograph.

All aspects of the manufacture and control of dihydrocodeine hydrogen tartrate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) certificate of suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce tablets containing either 20mg dihydrocodeine tartrate and 500mg paracetamol, or 30mg dihydrocodeine tartrate and 500mg paracetamol.

Satisfactory details of the pharmaceutical development of the medicinal products have been supplied. Suitable data have been provided to show that the dissolution properties of the products are satisfactory.

No excipients of animal or human origin are used in the final products.

None of the excipients are sourced from genetically modified organisms.

Manufacture of the product

A description and flow-chart of the manufacturing method have been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale and has shown satisfactory results. A validation protocol and a commitment to verify the first three production-scale batches have been provided.

Finished Product Specifications

The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months and storage conditions of "Do not store above 25 ºC. Store in the original package" for both strengths of product are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol and dihydrocodeine hydrogen tartrate are well-established. As these actives are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment (ERA). As these products are intended to be used interchangeably with other products that are currently on the market, it is not expected that environmental exposure will increase following approval of these marketing authorisations.

IV CLINICAL ASPECTS

IV.1 Introduction

No new data are required for these applications. The applicant's clinical overview on the clinical pharmacology, efficacy and safety of the product has been written by an appropriately qualified person and is adequate.

IV. 2 Pharmacokinetics

According to the regulatory requirements, CPMP/EWP/QWP/1401/98 NfG on the *Investigation of Bioavailability and Bioequivalence*, no new pharmacokinetic data are required to support these applications.

IV.3 Pharmacodynamics

No new pharmacodynamic data are required to support these applications and none have been submitted.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

No new data have been submitted with these applications.

IV.6 Risk Management Plan (RMP)

A suitable pharmacovigilance system and a risk management plan have been submitted.

A summary of the risk minimisation measures is provided below:

Important identified risks

Safety Concern	What is Known	Preventability
Allergic to paracetamol, dihydrocodeine or any other ingredients in these tablets. (Hypersensitivity)	Allergic reactions can include sudden wheeziness, difficulties in breathing, swelling of the eyelids, face or lips, rash or itching.	You must not take Co-dydramol Tablets if you are allergic to any of the ingredients. If any of these reactions occur patients should tell your doctor straight away.
Patients with breathing problems or lung disease which makes breathing difficult.	There is an increased risk of developing serious and life-threatening complications of the breathing problems or lung disease.	You must not take Co-dydramol Tablets if you have breathing problems or lung disease which makes breathing difficult.
Regular prolonged use of dihydrocodeine is known to lead to addiction and tolerance.	Symptoms of restlessness and irritability may result when the treatment is stopped. The side effects can depend on the individual, the drug used, the size and frequency of the dose, and how long the drug has been taken.	Do not take this medication for longer than is completely necessary. Your doctor should inform you of the risks of addiction and that long-term use should be avoided. If you have taken regular daily doses for a long time, do not suddenly stop treatment without discussing this with your doctor as you may experience withdrawal effects.
Taking these tablets for headaches too often or for too long can make them worse.	Taking painkillers too often or for too long can result in medication-overuse headaches. The body gets used to the painkillers. Rebound headaches can develop within a day or so of the last dose.	You should take the tablets as prescribed by your doctor. If your pain persists then talk to your doctor.
These tablets may affect your ability to drive safely or operate machinery.	Co-dydramol tablets can make patients feel drowsy, dizzy and sleepy. It is an offence to drive if this medicine affects your ability to drive.	Do not drive while taking this medicine until you know how it affects you. If these tablets make you feel drowsy, do not drive or operate machinery. Co-dydramol Tablets can affect your ability to drive as they may make you sleepy or dizzy.
Overdose	Taking too much paracetamol can cause serious liver damage and in some cases this can be fatal. There may not necessarily be any symptoms in the early stages of an overdose.	Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. If you have taken more of this medicine than you should then contact doctor at once, even if you have no symptoms

Important potential risks

Safety Concern	What is Known
Caution is advised in patients with allergic disorders	Allergic reactions can include sudden wheeziness, difficulties in breathing, swelling of the eyelids, face or lips, rash or itching.
The tablets should not be taken by a patient during an asthma attack.	The patient would have an increased risk of developing serious and life-threatening adverse reactions.
Caution is advised if there is a marked impairment of liver function, in those with chronic hepatic disease and in persistent heavy drinkers; the amount taken should be reduced.	These tablets may cause liver problems to be more severe. Alcohol increases the risk of liver damage that can occur if an overdose of paracetamol is taken. The hazards of paracetamol overdose are greater in persistent heavy drinkers and in people with alcoholic liver disease. An overdose can cause liver failure.
Caution is advised if there is advanced kidney disease.	These tablets may cause kidney problems to be more severe.
Caution is advised in patients taking a medicine known as monoamine oxidase inhibitors (e.g. tranylcypromide, phenelzine, isocarboxazid, moclobemide and linezolid.)	Opioids should not be taken within 14 days of monoamine oxidase inhibitors due to the potential for severe low blood pressure, effects on breathing and on the central nervous system. Use at the same time may cause serotonin syndrome.
Other paracetamol containing products should not be taken at the same time.	An overdose of paracetamol can cause delayed, serious liver damage. An overdose of Paracetamol can lack significant early symptoms. Symptoms can include sickness, stomach pain and a pale colouring of skin.
Taking medicines that depress the central nervous system (CNS depressants e.g. sedative or anti-depressant medicines) or drinking alcohol while taking this medicine	The effect of medicines that depress the central nervous system (and the effect of alcohol) may be increased by dihydrocodeine which could mean breathing, heart rhythm and circulation is slowed.
The amount taken should be reduced in the elderly and in those with an under active thyroid gland.	In these patients Co-dydramol may have a stronger effect and a longer duration of action than predicted. An overdose can cause liver failure.
Use should be avoided in patients with increased pressure in their skull (for instance due to brain disease) or have a head injury.	These tablets may make these symptoms worse or hide the extent of an injury.
Caution is advised in patients with an enlarged prostate	Dihydrocodeine may cause a lack of ability to urinate, which is already a common complication of an enlarged prostate
Use of Co-dydramol Tablets during pregnancy.	If used during labour it may cause breathing difficulties in the baby after birth. If dihydrocodeine is used regularly in the third trimester it may cause withdrawal symptoms in the baby after birth.

Missing information

Safety Concern	What is Known
Use in children under 12 years of age	The use of this product is not recommended for children under 12 years of age and so there is no experience of its safety and efficacy in this age group.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A user consultation with target patient groups on the PIL has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applications include an adequate review of published non-clinical and clinical data concerning the efficacy and safety of paracetamol and dihydrocodeine hydrogen tartrate.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

The currently approved labels are provided below:

PP2413

CO-DYDRAMOL 20/500mg TABLETS
Dihydrocodeine Paracetamol M&A Pharmachem Ltd
CO-DYDRAMO 20/500mg TABLETS
Dihydrocodeine Paracetamol M&A Pharmachem L


Co-dydramol
56 Tablets 30/500 mg Tablets
Please read the patient information leaflet before use.
Tablets for oral administration. Swallow the tablets with a glass of water. To be taken as directed by the physician.
• 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 dihydrocodeine regularly for a long time can lead to addiction.
• 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.
Each tablet contains:
Dihydrocodeine Tartrate 30 mg
Paracetamol 500 mg.
Contains paracetamol
Keep out of the sight and reach of children.
This medicine can make you feel sleepy. Do not drive while taking this medicine until you know how it makes you feel. See the leaflet inside for more information.
Do not store above 25°C.
Store in the original package.
PHARMACY USE ONLY
POM
PL 04077/0244
PIP 119-9223
Manufacturer and MA Holder:
M & A PHARMACHEM LTD
BOLTON BL5 2AL, ENGLAND
CO-DYDRAMOL
#30/#500 MG
TABLETS
Co-Dydramol
56 Tablets
Capsule-Shaped Tablets
New advice for drivers - see leaflet inside
Co-Dydramol
30/500 mg
Tablets
Dihydrocodeine
Paracetamol
M & A Pharmachem
Co-Dydramol
30/500 mg
Tablets
M & A Pharmachem
56 Tablets
5 014363 082615
PP2410


CO-DYDRAMOL 30/500mg TABLETS
Dihydrocodeine Paracetamol M&A Pharmachem Ltd

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)