Public Assessment Report

Co-Codamol 30/500 Effervescent Tablets

Paracetamol 500mg
Codeine Phosphate Hemihydrate 30mg

PL 15833/0025

Manx Pharma

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Lay Summary

The MHRA granted Manx Pharma a Marketing Authorisation (licence) for the medicinal product Co-Codamol 30/500 Effervescent Tablets (PL 15833/0025) on the 14th September 2007. The product is indicated in the relief of severe pain.

Co-Codamol 30/500 Effervescent Tablets contains the active ingredients paracetamol and codeine. Co-Codamol 30/500 Effervescent Tablets was considered the same as the original product Solpadol (Sanofi-Synthelabo Ltd, PL 11723/0072) based on the Quality profile, as the product is an oral solution a bioequivalence study was judged not to be necessary. It was judged that the benefits of taking Co-Codamol 30/500 Effervescent Tablets outweighed the risks, hence a Marketing Authorisation was granted.
Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal product Co-Codamol 30/500 Effervescent Tablets (Pl 15833/0025) on the 14th September 2007. Co-Codamol 30/500 Effervescent Tablets were shown to correspond to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance and the same dosage form to the reference product Solpadol (Sanofi-Synthelabo Ltd, PL 11723/0072).

Co-Codamol 30/500 Effervescent Tablets are indicated in the treatment of severe pain and are a prescription only medicine.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

1. Paracetamol

Nomenclature

INN: Paracetamol Ph Eur 500 mg

Chemical names: Paracetamol;
       Acetaminophen
       N-Acetyl-p-aminophenol
       Paracetamolum
       4'-hydroxyacetanilide
       N-(4-hydroxyphenyl)acetanilide

Structure

A current certificate of suitability was provided for the source of the drug substance paracetamol. The certificate of suitability indicates that:

An appropriate specification has been provided.
Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Paracetamol is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated.

2 Codeine

Nomenclature

Chemical Names
Codeine Phosphate Hemihydrate;
Codeini Phosphas Hemihydricus
Methylmorphine phosphate hemihydrate

Structure

A current certificate of suitability was provided for the source of the drug substance codeine. The certificate of suitability indicates that:

An appropriate specification has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Codeine is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated.
DRUG PRODUCT

Composition of Drug Product

Paracetamol
Codeine
Sodium hydrogen carbonate
Anhydrous sodium carbonate
Anhydrous citric acid
Sodium docusate
Sorbitol (E420)
Saccharin sodium
Dimeticone
Sodium benzoate
Macrogol 6000

Natural grapefruit flavour
Essential oil of grapefruit
Concentrated lemon, orange, orange pulp and grapefruit juices
Gentian infusion
Cis-3-hexenol
Ethyl 2-methylbutyrate
Acacia gum
Maltodextrin
Butylated hydroxyanisole.

The pharmaceutical form was selected to enable good dissolution. All excipients comply with the PhEur and certificates of analysis have been provided bar the Grapefruit flavour, satisfactory specifications were provided for this excipient which is compliance with EU directives. There are no excipients of animal or human origin, the magnesium stearate used is of plant origin. There were no novel excipients used and no overages.

Dissolution and impurity profiles
Dissolution of and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacture
A description and flow-chart of the manufacturing method has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of the drug product. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.
Container Closure System
Primary packaging for the tablets is either Al/PE blister strips or round tubes of white PP closed with a PE stopper and containing a desiccant cartridge.

Stability
Satisfactory stability data was provided to support the shelf-life of two years under the following storage conditions

- Protect from moisture
- Protect from light
- Store in the original packaging
- Do not store above 25°C

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
A Marketing Authorisation was granted.
PRE-CLINICAL ASSESSMENT

No pre-clinical data were provided for this application and none were required.
MEDICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Co-codamol is a compound analgesic preparation containing codeine phosphate and paracetamol.

Pharmacodynamics

Paracetamol has analgesic and antipyretic actions similar to those of aspirin with weak anti-inflammatory effects. Paracetamol is only a weak inhibitor of prostaglandin biosynthesis, although there is some evidence to suggest that it may be more effective against enzymes in the CNS than those in the periphery. This fact may partly account for its well documented ability to reduce fever and induce analgesia, effects that involve actions on the neural tissues.

Codeine is an analgesic with uses similar to those of morphine but has only mild sedative effects. The major effects of codeine are on the CNS and the bowel. However, its effects are remarkably diverse and include analgesia, drowsiness, changes in mood, respiratory depression and decreased gastrointestinal motility. The relief of pain is relatively selective, in that other sensory modalities (touch, vibration, vision, hearing etc.) are not obtunded.

Pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal tract with a peak plasma concentration occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma protein binding is negligible at the usual therapeutic concentrations but increases with increasing concentrations.

Codeine and its salts are absorbed from the gastrointestinal tract. Peak plasma codeine concentrations occur about an hour following ingestion. It is metabolised by O- & N-demethylation in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half-life has been reported to be between 3 and 4 hours after oral administration.

Bioequivalence

The applicant submitted a detailed report justifying the absence of a bioequivalence study and this was found to be satisfactory.

EFFICACY

The applicant has submitted a report of an open multi-centre study which evaluated the acceptability of the present pharmaceutical preparation of paracetamol and codeine effervescent tablets in 30 adults (aged 24-82 years) in normal conditions of use. The subjects received 1 to 2 effervescent tablets of paracetamol (500mg) and codeine (30 mg), 1 to 3 times per day, for 3 to 5 days. The results concerning the
global acceptability of the tablets and the opinion of the taste of the solution are summarized in tables 1 and 2 below:

**Table 1: global acceptability of the tablets**

<table>
<thead>
<tr>
<th>Global acceptability</th>
<th>Frequency</th>
<th>Percent</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>completely</td>
<td>13</td>
<td>43.3</td>
<td>[25.5-62.6]</td>
</tr>
<tr>
<td>rather yes</td>
<td>12</td>
<td>40.0</td>
<td>[22.7-59.4]</td>
</tr>
<tr>
<td>rather no</td>
<td>5</td>
<td>16.7</td>
<td>[5.7-34.7]</td>
</tr>
</tbody>
</table>

**Table 2: Taste of the solution**

<table>
<thead>
<tr>
<th>Taste</th>
<th>Frequency</th>
<th>Percent</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>good</td>
<td>7</td>
<td>23.3</td>
<td>[9.9-42.3]</td>
</tr>
<tr>
<td>quite good</td>
<td>14</td>
<td>46.7</td>
<td>[28.3-65.7]</td>
</tr>
<tr>
<td>not very good</td>
<td>7</td>
<td>23.3</td>
<td>[9.9-42.3]</td>
</tr>
<tr>
<td>bad</td>
<td>2</td>
<td>6.7</td>
<td>[0.8-22.1]</td>
</tr>
</tbody>
</table>

The global acceptability of the tablets was judged as good by more than 83% of the patients; the opinion of the taste of the solution was good for 71% of the subjects. Moreover, 70% of the patients were satisfied for the speed of the effervescent tablets dissolution.

The symptom evolution was judged as satisfactory for 20 subjects by investigators (66%) and for 21 subjects (77%) by the patients, without discrepancy between the investigators and the patients.

The applicant has also submitted copies of several publications with a summary review of the literature confirming the effectiveness of Co-codamol effervescent tablets.

**SAFETY**

In the study report mentioned above submitted with this application, ten patients (33%) experienced a total of 15 adverse events. All adverse events were well-known side effects qualified as probably (n=11) or possibly (n=4) related to the tested active ingredients: drowsiness: n=5, nausea: n=4, dry mouth: n=5, dizziness: n=1, constipation: n=1, abdominal pain: n=1. No serious adverse were reported.

The applicant has also provided several copies of publications with a safety review from the literature. No new safety issues have been detected.

**EXPERT REPORT**

A satisfactory Clinical Expert Report has been submitted with appropriate brief CV.
SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

CONCLUSIONS
A Marketing Authorisation may be granted for this product.
Overall Conclusion and Risk/Benefit Analysis

Quality
The quality characteristics of Co-Codamol 30/500 Effervescent Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Pre-Clinical
No new preclinical data were submitted and none are required for applications of this type.

Efficacy
Efficacy has been demonstrated for this product. A satisfactory justification for the absence of a bioequivalence study was provided. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for

Risk/Benefit Analysis
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.
Steps Taken During Assessment

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<tr>
<td>1</td>
<td>The MHRA received the application on 7th October 2004.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 20th October 2004.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 6th June 2005, 29th March 2006, 22nd May 2005 and on the medical assessment on 1st July 2005.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 9th January 2006, 17th May 2007 and 2nd July 2007 and on the medical assessment on 9th January 2006.</td>
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<tr>
<td>5</td>
<td>The application was determined on 14th September 2007.</td>
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Steps Taken after Assessment
None
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Co-Codamol 30 mg/500 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each effervescent tablet contains:
Paracetamol 500.0mg
Codeine Phosphate Hemihydrate 30.0mg
Excipients: sorbitol (E420)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Effervescent Tablet
White, bevelled, flat, round tablets with a scoreline on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the relief of severe pain.

4.2 Posology and method of administration
Co-codamol 30 mg/500 mg Effervescent Tablets are given orally and should be dissolved in at least half a tumbler-full of water before taking.
Adults: One or two effervescent tablets every 4-6 hours, up to a maximum of 8 tablets in any 24 hour period.
Elderly: As for adults, however a reduced dose may be required. See warnings.
Children: Not recommended for children under 12 years of age.

4.3 Contraindications
Hypersensitivity to paracetamol or codeine which is rare, or hypersensitivity to any of the other constituents. Conditions where morphine and opioids are contraindicated e.g., acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure and following biliary tract surgery; monoamine oxidase inhibitor therapy, concurrent or within 14 days.

4.4 Special warnings and precautions for use
Each tablet contains 410mg sodium (17.83mEquivalents). This sodium content should be taken into account when prescribing for patients in whom sodium restriction is indicated.
Care should be observed in administering the product to any patient whose condition may be exacerbated by opioids, particularly the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS...
depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease.

As this medicine contains sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine.

Patients should be advised not to exceed the recommended dose and not take other paracetamol containing products concurrently.

4.5 Interaction with other medicinal products and other forms of interaction
Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

The effects of CNS depressants (including alcohol) may be potentiated by codeine.

4.6 Pregnancy and lactation
There is inadequate evidence of the safety of codeine in human pregnancy, but there is epidemiological evidence for the safety of paracetamol. Both substances have been used for many years without apparent ill consequences and animal studies have not shown any hazard. Nonetheless careful consideration should be given before prescribing the products for pregnant patients. Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.

Paracetamol is excreted in breast milk but not in a clinically significant amount.

4.7 Effects on ability to drive and use machines
Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

4.8 Undesirable effects
Codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, confusion, drowsiness and urinary retention. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity. Tolerance and dependance can occur, especially with prolonged high dosage of codeine.

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
4.9 **Overdose**

**Codeine:**
The effects of Codeine overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

**Symptoms**
Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

**Management**
Management should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350mg of codeine or a child more than 5mg/kg. Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

**Paracetamol:**
Patients in whom oxidative liver enzymes have been induced, including alcoholics and those receiving barbiturates and patients who are chronically malnourished, may be particularly sensitive to the toxic effects of paracetamol in overdose.

**Symptoms**
Symptoms of paracetamol overdosage in the first 24 hours are 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, coma and death. 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 likely in adults who have taken 10g 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.

**Management**
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Any patient who has ingested in excess of 150mg/kg or 12g within the previous hour should receive activated charcoal. Intravenous acetylcysteine is beneficial when given up to 24 hours after the ingestion of paracetamol, if more than 24 hours have elapsed since the overdose expert advice should be sought regarding appropriate management. Oral methionine may be given if acetylcysteine is not available as long as the overdose has been taken within the previous 10-12 hours and the patient is not vomiting. General supportive measures must be available.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol’s lack of appreciable anti-inflammatory activity. Paracetamol exhibits antipyretic activity.
Codeine is a centrally acting analgesic which produces its effects by its action at opioid binding sites (m-receptors) within the CNS. It is a full agonist.

5.2 Pharmacokinetic properties
Following oral administration of two effervescent tablets (i.e., a dose of paracetamol 1000mg and codeine 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 20.4mg/ml and 218.8ng/ml respectively. The mean times to maximum plasma concentrations were 0.34 hours of paracetamol and 0.42 hours for codeine phosphate.
The mean AUC for the 10 hours following administration was 50.0mg.ml⁻¹.h for paracetamol and 450.0 ng/ml⁻¹.h for codeine.
The bioavailabilities of paracetamol and codeine when given as the combination are similar to those when they are given separately.

5.3 Preclinical safety data
There are no preclinical data of relevance which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet
Sodium hydrogen carbonate
Anhydrous sodium carbonate
Anhydrous citric acid
Sodium docusate
Sorbitol (E420)
Saccharin sodium
Dimeticone
Sodium benzoate
Macrogol 6000
Natural grapefruit flavour
Essential oil of grapefruit
Concentrated lemon, orange, orange pulp and grapefruit juices
Gentian infusion
Cis-3-hexenol
Ethyl 2-methylbutyrate
Acacia gum
Maltodextrin
Butylated hydroxyanisole.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container
Aluminium/polyethylene blister strips (30 micron aluminium strip with internal polyethylene coating) containing 4 or 10 tablets per strip in an outer cardboard carton. Pack sizes of 28, 30, 50, 56 and 100. White polypropylene tubes sealed with a polyethylene stopper containing a desiccant cartridge in an outer cardboard carton. Tube sizes of 8, 10 and 16 tablets. Pack sizes of 10, 16, 32 and 96 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Manx Pharma
Taylor Group House
Wedgnock Lane
Warwick
CV34 5YA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 15833/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/09/2007

10 DATE OF REVISION OF THE TEXT
Leaflet and Labels

Co-codamol 30mg/500mg Effervescent Tablets (Paracetamol and Codeine Phosphate Hydrochloride) Information for the User

Read all of this leaflet carefully before you start taking this medicine.

1. Keep the leaflet. You may need to refer to it again.
2. If you have further questions, please ask your doctor or your pharmacist.
3. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
4. If any of the side effects get worse, or if you notice any effects not listed in this leaflet, please tell your doctor or pharmacist.

What is Co-codamol 30mg/500mg Effervescent Tablets?

It contains paracetamol and codeine phosphate hydrochloride which are included to be the active ingredients in the tablets and to be free of other substances. These substances are excipients, such as inactive ingredients, which are the substances that are used to make the tablets, such as sodium carbonate, anhydrous sodium chloride, sodium bicarbonate, potassium chloride, magnesium oxide, and talc. These substances are added to the tablets to ensure that they are not harmful to the body and that they do not interfere with the way the tablets work.

The active substance is paracetamol, which is an analgesic and antipyretic. It reduces fever and pain by inhibiting the synthesis of prostaglandins, which are responsible for the release of inflammatory mediators.

This leaflet contains information about the active ingredients of Co-codamol 30mg/500mg Effervescent Tablets, including the concentration of each ingredient. It also contains information about the inactive ingredients and the potential side effects of the tablets. It is important to read this leaflet carefully before taking the tablets to ensure that you are aware of all the information you need to be able to make an informed decision about whether or not to take the tablets.

What is the active substance of Co-codamol 30mg/500mg Effervescent Tablets?

The active substance is paracetamol, which is an analgesic and antipyretic. It reduces fever and pain by inhibiting the synthesis of prostaglandins, which are responsible for the release of inflammatory mediators.