CO-CODAMOL 8/500 TABLETS
PL 17780/0510

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Winthrop Pharmaceuticals UK Limited a Marketing Authorisation (licence) for the medicinal product Co-codamol 8/500 Tablets (PL 17780/0510) on 15th January 2010. This is a prescription-only medicine.

Co-codamol 8/500 Tablets contains two active ingredients- paracetamol and codeine both of which belong to a group of medicines called pain-killers (analgesics). Co-codamol 8/500 Tablets is a “compound analgesic” and is used to treat headache, including migraine, toothache, neuralgia, period pain, pain caused by rheumatism and arthritis and to relieve symptoms of cold, flu and sore throats.

This application is identical to the previously granted application for Co-codamol 8/500 Tablets (PL 17780/0071), granted to Winthrop Pharmaceuticals UK Limited on 13th November 2001. Essential similarity or equivalence to the approved product has been demonstrated and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Co-codamol 8/500 Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

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Based on the review of the data on quality, safety and efficacy, the MHRA granted Winthrop Pharmaceuticals UK Limited a Marketing Authorisation for the medicinal product Co-codamol 8/500 Tablets (PL 17780/0510) on the 15th January 2010. The product is prescription-only medicine.

This application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC, cross-referring to Co-codamol 8/500 Tablets currently granted to Winthrop Pharmaceuticals UK Limited (PL 17780/0071). This product has previously been shown to be essentially similar to the originator product Co-codamol Tablets (PL 00071/5073R) licensed to Smithkline Beecham (SWG) Limited in November 1981.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for it.

The product contains the active ingredients paracetamol and codeine which are indicated for pain relief.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 17780/0510
PROPRIETARY NAME: Co-codamol 8/500 Tablets
ACTIVE(S): Codeine Phosphate Hemihydrate
Paracetamol
COMPANY NAME: Winthrop Pharmaceuticals UK Limited
E.C. ARTICLE: Article 10c of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION
This is a simple, informed consent application for Co-codamol 8/500 Tablets submitted under Article 10c of Directive 2001/83/EC. The proposed Marketing Authorisation Holder is Winthrop Pharmaceuticals UK Limited, One Onslow Street, Guildford, Surrey, GU1 4YS, UK.

The application cross-refers to Co-codamol 8/500 Tablets (PL 17780/0071), approved on 13th November 2001 to the same marketing authorisation holder Winthrop Pharmaceutical UK Limited. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed name of the product is Co-codamol 8/500 Tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
This product contains codeine phosphate hemihydrate and paracetamol equivalent to 8mg and 5000mg respectively. Co-codamol 8/500 Tablets are to be stored in child-resistant blisters composed of aluminium and polyvinylchloride in pack sizes of 50 and 100 tablets. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed. All primary product packaging complies with EU legislation regarding contact with food. The proposed shelf-life is 5 years with no specific storage conditions is consistent with the details registered for the cross-reference product.

2.3 Legal status
The product will be available as a prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Winthrop Pharmaceuticals UK Limited, One Onslow Street, Guildford, Surrey, GU1 4YS, UK.
The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.
2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference products.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification

The proposed finished product specifications are in-line with the details registered for the cross-reference product.

2.9 Drug substance specification

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance

None of the excipients used in the product contain materials of animal or human origin. This is consistent with the cross-reference product.

3. EXPERT REPORTS

The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product names. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed summary is consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/CARTON

The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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.

Carton and blister

The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the
applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with this application are acceptable. A Marketing Authorisation should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Codeine and paracetamol are well known drugs and have been used in the treatment of pain relief for many years. This application is identical to previously granted application for Co-codamol 8/500 Tablets (PL 17780/0071) in which the applicant demonstrated essential similarity to the innovator product Co-codamol Tablets and (PL 00071/5073R) licensed to Smithkline Beecham (SWG) Limited.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product which, in turn, has been shown to be interchangeable with the innovator product. Extensive clinical experience with codeine and paracetamol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
CO-CODAMOL 8/500 TABLETS
PL 17780/0510

STEPS TAKEN FOR ASSESSMENT

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<td>The MHRA received the marketing authorisation application on 28&lt;sup&gt;th&lt;/sup&gt; October 2009.</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 5&lt;sup&gt;th&lt;/sup&gt; November 2009.</td>
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<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 7&lt;sup&gt;th&lt;/sup&gt; January 2010.</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on 7&lt;sup&gt;th&lt;/sup&gt; January 2010.</td>
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<td>The application was determined on 15&lt;sup&gt;th&lt;/sup&gt; January 2010.</td>
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CO-CODAMOL 8/500 TABLETS
PL 17780/0510

STEPS TAKEN AFTER ASSESSMENT

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Co-codamol 8/500 Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 500mg paracetamol and 8mg codeine phosphate.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablets
Flat, white tablets, with S/4 on one side and blank on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
This product is recommended for the relief of most painful and febrile conditions such as headache including migraine, neuralgia, toothache, sore throat, colds, influenza, dysmenorrhoea and rheumatic pain.

4.2 Posology and method of administration

Adults and children over 12 years:
Two tablets, to be taken with a glass of water, not more frequently than every 4 hours, up to a maximum of 8 tablets in any 24 hour period.

Children under 12 years:
Not recommended for children under 12 years of age.

The product is for oral administration.

4.3 Contraindications
Hypersensitivity to paracetamol, codeine phosphate or any of the other constituents.

4.4 Special warnings and precautions for use
Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

The recommended dose should not be exceeded. This medicine should not be taken with any other paracetamol-containing products. If symptoms persist, the patient should be advised to consult their doctor. The patient should be advised to see immediate medical advice in the event of an overdose, even if they feel well, because of the risk of delayed, serious liver damage.

The risk-benefit of continued use should be assessed regularly by the prescriber.

The leaflet will state in a prominent position in the 'before taking' section:
- Do not take for longer than directed by your prescriber
- Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets.
- Taking a painkiller for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack – not boxed):
- Do not take for longer than directed by your prescriber as taking codeine regularly for a long time can lead to addiction
4.5 Interaction with other medicinal products and other forms of interaction

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 daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

4.6 Pregnancy and lactation

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dose. Codeine has been used for many years without apparent ill consequence and animal studies have not shown any hazard. Patients should follow the advice of their doctor regarding the use of this product. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

- Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.
- Prolonged use of a painkiller for headaches can make them worse.

Blood and the lymphatic system
Frequency not known: blood dyscrasias including thrombocytopenia and agranulocytosis

Nervous system disorders
Frequency not known: dizziness, light-headedness, confusion, drowsiness

Gastrointestinal disorders
Frequency not known: pancreatitis, constipation, nausea, vomiting

Skin and subcutaneous tissue disorders
Frequency not known: allergic reactions (hypersensitivity) including skin rash

Renal and urinary disorders
Frequency not known: urinary retention

4.9 Overdose

Paracetamol
Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors
If the patient:
- is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John’s Wort or other drugs that induce liver enzymes, or
- regularly consumes ethanol in excess of recommended amounts, or
- is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

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, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.
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. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines (see BNF overdose section).

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Codeine
The effects in 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
This 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 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 four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anilides, Paracetamol combinations
ATC Code: N02B E51
Paracetamol is an analgesic and antipyretic.

Codeine phosphate is a moderate analgesic and has weak cough suppressant activity.

5.2 Pharmacokinetic properties
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Concentration in plasma reaches a peak in 30-60 minutes. Plasma half-life is 1-4 hours. Paracetamol is relatively uniformly distributed throughout most body fluids, plasma protein binding is variable.

Codeine phosphate is well absorbed after oral administration and is widely distributed. About 86% is excreted in the urine in 24 hours; 40-70% if free or conjugated morphine, 5-15% is free or conjugated norcodeine.

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

6.1 List of excipients
Maize starch
Povidone
Potassium sorbate
Microcrystalline cellulose
Stearic acid
Magnesium stearate
Talc
Pregelatinised starch
Purified water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
5 years

6.4 Special precautions for storage
Do not store above 25ºC.

6.5 Nature and contents of container
Blisters strips: 31.0 g/m2 - 45 g/m2 Glassine (pregamin) paper/9 micron soft temper Aluminium foil/250 micron PVC contained in cardboard cartons.

Pack sizes: 50 and 100 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
United Kingdom
Trading as: Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17780/0510

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/01/2010

10 DATE OF REVISION OF THE TEXT
15/01/2010
CO-CODAMOL 8/500 TABLETS
Codeine Phosphate and Paracetamol

PATIENT INFORMATION LEAFLET

Please read all of the information and warnings before you start any medical treatment. If you have any further questions, please ask your doctor or pharmacist. This leaflet does not cover all possible adverse reactions or interactions with other medicines. If you are, or think you may be, pregnant, or if you have any unusual symptoms, please consult your doctor or pharmacist before taking this medicine.

1. WHAT CO-CODAMOL IS AND WHAT IT IS USED FOR

CO-CODAMOL IS A COMBINED ANALGESIC PREPARATION USED FOR RELIEF OF MILD TO MODERATE PAIN. IT COMBINES CODEINE PHOSPHATE AND PARACETAMOL.

2. BEFORE YOU TAKE CO-CODAMOL

If you are pregnant or breastfeeding, you should not use CO-CODAMOL. It is not recommended for children under 12 years of age. CO-CODAMOL should only be used under medical supervision.

3. HOW TO TAKE CO-CODAMOL

Follow the instructions on the packaging. Do not exceed the recommended dose.

4. POSSIBLE INTERACTIONS

Consult your doctor or pharmacist before taking any other medicine with CO-CODAMOL.

5. POSSIBLE ADVERSE REACTIONS

Common side effects include:

- Dizziness
- Headache
- Nausea
- Lightheadedness

If you experience any of these side effects, please consult your doctor or pharmacist.

6. OVERDOSE

In the event of an overdose, please seek medical attention immediately.

7. STORE TIPS

Keep out of reach of children. Store in a cool, dry place.

8. FURTHER INFORMATION

For more information, please consult your doctor or pharmacist. 

9. LEGAL USE

This leaflet is only valid for the treatment of pain in adults and children over 12 years of age. CO-CODAMOL is available only on prescription.

10. PATIENT INFORMATION LEAFLET

This leaflet is a summary of the information provided by the manufacturer. Please read the full leaflet before taking CO-CODAMOL.
CO-CODAMOL 8/500 TABLETS
PL 17780/0510

LABELLING

CARTON

BLISTER FOIL