CO-CODAMOL 30/500MG EFFERVESCENCE TABLETS

PL 15582/0022

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Zanza Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Co-Codamol Effervescent Tablets 30/500mg (PL 15582/0022). This prescription only medicine (POM) is indicated for the relief of severe pain.

Co-Codamol Effervescent Tablets 30/500mg contain the active ingredients paracetamol and codeine, which are pain relievers. Pain relief preparations containing paracetamol and codeine, have been available in the UK for more than ten years.

No new or unexpected safety concerns arose from this standard application and it was, therefore, judged that the benefits of taking Co-Codamol Effervescent Tablets 30/500mg outweigh the risks, hence a Marketing Authorisation has been granted.

CO-CODAMOL 30/500MG EFFERVESCENCE TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisation for the medicinal product Co-Codamol Effervescent Tablets 30/500mg (PL 15582/0022) to Zanza Healthcare Limited on 7 March 2006. This product is a POM.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of EC Directives 65/65, cross-referring to Solpadol Effervescent Tablets (PL 11723/0072), approved on 2 October 1993. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.

Co-Codamol Effervescent Tablets is recommended for the treatment of severe pain that is not alleviated by paracetamol or asprin alone.

PHARMACEUTICAL ASSESSMENT REPORT

Introduction

Legal Basis

These applications are submitted under Article 10.1(a)(iii) of EC Directives 65/65, as amended, claiming essential similarity to Efferalgan Codéine 500mg/30mg Comprimé Effervescent Sécable, granted marketing authorisation in France in 1988. The reference medicinal product is Solpadol Effervescent Tablets (PL 11723/0072). This product was first marketed on 2 October 1993 in the UK, therefore the 10 year rule for registration in the EU of "essentially similar" products has been fulfilled.

Use (and Possible Justification)

Paracetamol and codeine are analgesics. The indication "for the relief of severe pain" is the same as Solpadol Effervescent 500mg/30mg.

Name and Appearance

The generic name Co-codamol 30/500mg Effervescent Tablets is acceptable. The tablets are white, bevelled, flat and round, with a score line. There are no distinguishing markings.

Composition

Qualitative Composition of the Medicinal Product

Substance	**Ref./ monograph**	**Function**
Paracetamol	Ph.Eur.	Active substance
Codeine phosphate hemihydrate	Ph.Eur.	Active substance
Sodium hydrogen carbonate	Ph.Eur.	Carbonate: effervescent agent
Sodium carbonate, anhydrous	Ph.Eur.	Carbonate: effervescent agent
Citric acid , anhydrous	Ph.Eur.	Organic acid: effervescent agent
Sodium docusate	Ph.Eur.	Surfactant
Sorbitol, Neosorb P60W	Ph.Eur.	Diluent sweetner
Saccharin sodium	Ph.Eur.	Antifoam
Dimeticone 50cp	Ph.Eur.	Lubricant
Sodium benzoate, micronized	Ph.Eur.	Lubricant
Macrogol 6000	Ph.Eur.	Lubricant
Spray-dried natural grapefruit flavour, Code No: 862404	In-house	Flavour
Purified water (removed during drying)	Ph.Eur.	Granulation solvent

Container

The container for this product is a PP tablet container with a PE stopper containing silica gel as desiccant.

Clinical Trial Formula

Not applicable. It is stated that as the tablet forms a solution, no biostudy is required. This is accepted. The disintegration time of Efferlan Codeine (70 seconds and 75 seconds) and the applicant product (74 seconds, 83 seconds and 89 seconds) was compared. These results are comparable.

Development Pharmaceutics

The development pharmaceutics was fairly well presented and the issues addressed included the rationale for the formulation and its subsequent evolution. Codeine is freely soluble in water but paracetamol is only sparingly soluble. The solubility of paracetamol in the formulation has not been formerly assessed and a fine grade powder is used.

Key properties were seen as effervescence and flavour masking. Various formulations were assessed against the following criteria: hardness, disintegration, and appearance and taste of solution. The optimal was selected. Flavour and sweetening were further optimised in trials.

Levels of wetting agent and of antifoaming agent were optimised by trials.

A lubricant that produced good tabletting properties as judged by hardness, sticking, seizure and capping was selected.

Method of Preparation

The site of finished product manufacture carries a valid Good Manufacturing Practice (GMP) certificate. Batch release, assembly and quality control will also take place at this site.

The manufacturing formulas have been provided and are correct.

The manufacture of the product is relatively simple and uses conventional pharmaceutical methods. A flow chart of the manufacturing process has been provided. The account of the process is generally satisfactory.

The in-process controls applied are generally appropriate and appear to give a reproducible product.

Validation

The manufacturing process was appropriately validated. Some out of specification assay results were noted, which are believed to be due to mix separation during transfer to an external laboratory. However, all results were compliant during validation of a fourth batch that was assayed on-site.

An industrial scale validation plan is planned to follow marketing authorisation, this validation will take place on the first three industrial batches.

Control of Active Substances

The active ingredient paracetamol is manufactured by a supplier from which a Certificate of Suitability has been supplied.

Details of the specifications for routine controls of paracetamol by the finished product manufacturer have been provided and are acceptable.

The active ingredient codeine phosphate hemihydrate is manufactured by a supplier from which a certificate of suitability has been supplied.

Certificates show consistent results within specficiations.

Control of Excipients

Satisfactory certificates of analysis are supplied for ingredients controlled by the Ph.Eur.

Spray-dried Natural Grapefruit Flavour 86.2404 is the only ingredient not controlled by the Ph.Eur. A certificate of analysis is supplied by the manufacturer and the tablet manufacturer demonstrating compliance with the specification. Food grade certification is provided stating compliance with Directive 88/388/EEC.

Details of testing that will be performed routinely on excipients by the product manufacturer have been provided.

Packaging

The tubes are Borealis made of white polypropylene with a stopper containing a desiccant cartridge. Confirmation that the tube complies with the Ph.Eur. monograph for plastic containers and closures has been provided. The plastic complies with 90/128/EC. The desiccant stoppers containing silica gel complies with the Commission of the European Communities' positive list for additives used in food. The plastic complies with 90/128/EEC.

In Great Britain pack sizes of 30 (2 tubes of 15 tablets) and 100 tablets (5 tubes of 20 tablets) will be marketed. The first three industrial batches to be validated and put on stability will be packed in these tubes. Results of these tests will be provided post-approval.

Satisfactory supplier's certificates of packaging materials have been provided.

Finished product specification

There is a BP monograph for Effervescent Co-codamol Tablets.

It is noted that the MHRA has allowed the absence of tablet marking for effervescent tablets before due to tabletting issues.

The requirements of the BP monograph Co-codamol Effervescent Tablets has been fulfilled.

The HPLC technique employed measures both codeine and paracetamol. Satisfactory methodology is supplied which is different to the pharmacopoeial method. Satisfactory assay validation has been supplied. It is demonstrated that excipients do not interfere and that that paracetamol and codeine are adequately differentiated. Linearity has been adequately demonstrated between 80-120% of nominal. Precision and intermediate precision (different days) show satisfactory results for both paracetamol and codeine.

Batch Data

Three batches - ML060, ML061 and ML062 - are analysed. Each batch is one third of the size of a full production scale batch. The results seem consistent.

Batch analysis to the specifications has been provided.

Stability

It is stated that both actives will be re-tested every 2 years. Satisfactory stability data for both actives; under normal ICH conditions (25°C ± 2°C and 60% RH ± 5%) shows that paracetamol and codeine phosphate hemihydrate are stable for up to five and four years, respectively. Therefore, a re-test period of 2 years for both actives, when stored in normal conditions, is acceptable.

The assay for 4-aminophenol is described. It is not HPLC as described in the Ph.Eur. paracetamol monograph. It is a colorimetric reaction with nitroprusside to form a blue colour. It is demonstrated that the LOD is 25ppm.

A two year shelf life has been proposed and is acceptable.

24 months' stability data for the same batches shown in batch analysis are provided, stored in either polypropylene tubes or aluminium/polythene blisters.

In the tubes, disintegration is seen to increase with time, but remains within specification. A small decrease in paracetamol is seen (about 2%) over the same time period. Codeine does not appear to change. Hardness increases but remains within specification.

Expert Report

An expert report written by a pharmacist considered to be appropriately qualified has been provided and is satisfactory.

SPC, PILs and labels

The Summary of Product Characteristics (SPC) has instructions on dissolving the tablet and the sodium content is stated. This is acceptable. The Patient Information Leaflet (PIL) and labels for this product are satisfactory.

Conclusion

There are no pharmaceutical objections to the grant of a marketing authorisation.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a mainstream, national, abridged, standard licensing application submitted under article 10.1(a)(iii) of EEC Directive 2001/83/EC. The applicant claims essential similarity to Solpadol Effervescent Tablets (PL 11723/0072) (Sanofi-Synthelabo Limited), UK licence granted in October 1993.

2. BACKGROUND

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

3. INDICATIONS

For the relief of severe pain.

Assessor's Comment

This indication is consistent with that of the cross-referenced product licence.

4. DOSE & DOSE SCHEDULE

These are in line with those of the cross-referenced product licence.

5. TOXICOLOGY

No new data are submitted or required.

6. CLINICAL PHARMACOLOGY

6.1 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.

6.2 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 gastro intestinal tract. Peak plasma codeine concentrations occur about an hour following ingestion. It is metabolised by O- and 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.

6.3 Bioequivalence

No bioequivalence study data have been submitted. This is acceptable for the following reasons:

- Both drugs are sufficiently solved in water and have an unproblematic bioavailability. Therefore, paracetamol and codeine belong to the BCS-classification group I, for which bioequivalence testing can normally be waived.
- The paracetamol / codeine effervesecent tablet contains no inactive ingredient that is known to significantly affect absorption of the active drugs.
- The effervescent tablet is quickly soluble, the paracetamol / codeine is administered as solution.
- There exists no pharmacokinetic interaction between paracetamol and codeine.
- The pharmacokinetic profiles of paracetamol and codeine are comparable, since both drugs are rapidly absorbed and have very close plasma elimination half-lives.

With respect to the *Note of Guidance, Investigation of Bioavailability and Bioequivalence, 2001,* products as a liquid aqueous form in solution need not be involved in suitable bioequivalence studies under certain circumstances. This is applicable to paracetamol plus codeine effervescent tablets containing both active ingredients in aqueous solution before administration, despite the fact that paracetamol and codeine are not contained in a defined concentration – but in a defined amount – since the amount of water added may be variable. In addition, with these paracetamol plus codeine formulations there is no risk of bioinequivalence or pharmacotherapeutic failure or diminished clinical safety.

Assessor's Comment

The reason for not submitting bioequivalence study data has been fully justified and supported by the relevant clinical expert discussion and is acceptable.

7. 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

Global acceptability	**Frequency**	**Percent**	**95% CI**
Completely	13	43.3	[25.5-62.6]
Rather yes	12	40.0	[22.7-59.4]
Rather no	5	16.7	[5.7-34.7]

Table 2: Taste of the solution

Taste	**Frequency**	**Percent**	**95% CI**
Good	7	23.3	[9.9-42.3]
Quite good	14	46.7	[28.3-65.7]
Not very good	7	23.3	[9.9-42.3]
Bad	2	6.7	[0.8-22.1]

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 about the speed of the effervescent tablets dissolution.

The symptom evolution was judged to be 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 Effeverscent Tablets.

Assessor's Comment

The results of this study show that this formulation is generally well tolerated.

8. 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 events 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.

9. EXPERT REPORT

A satisfactory Clinical Expert Report has been submitted with appropriate brief CV.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The text of the summary of product characteristics is essentially similar to that of the cross-referenced product licence. However, for clarity, paragraphs should be separated by a space throughout the text of the SPC.

11. PATIENT INFORMATION LEAFLET

This is satisfactory.

12. LABELLING

Full colour mock-ups have been provided.

13. DISCUSSION

Compound analgesic preparations containing paracetamol and codeine, including Co-codamol, have been available in the UK for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

12. CONCLUSION

Marketing authorisation may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Co-Codamol 30/500 mg 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.

PRECLINICAL

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

EFFICACY

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 similar to the cross-reference product. The risk benefit ratio is considered to be positive.

CO-CODAMOL 30/500MG EFFERVESCENCE TABLETS

PL 15582/0022

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 1 March 2003
2	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 31 October 2003 and to the quality dossier on 7 November 2003
3	The applicant responded to the MHRA's requests, providing further information in June 2004
4	Following assessment of the response the MHRA requested further information relating to the quality dossier on 18 July 2005
5	The applicant responded to the MHRA's requests, providing further information on 30 August 2005
6	Following assessment of the response the MHRA requested further information relating to the quality dossier on 13 September 2005
7	The applicant responded to the MHRA's requests, providing further information on 19 January 2006
8	The application was determined on 7 March 2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Co-Codamol 30/500 mg Effervescent Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains:
30 mg of codeine phosphate hemihydrate (codeine base 22.5 mg) and
500 mg of paracetamol.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablets

White, bevelled, flat, round tablets with a break-line 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 30/500 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 not more frequently than every 4 hours, up to a maximum of 8 capsules or 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 effervescent tablet contains 410mg sodium (17.83m Equivalents). 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.

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

4.5. Interactions 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 dependence 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

Nausea and vomiting are prominent symptoms of codeine toxicity and if there is evidence of circulatory and respiratory depression, suggested treatment is gastric lavage and catharsis. If CNS depression is severe, assisted ventilation, oxygen and parenteral naloxone may be needed.

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 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.

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 and any patient who had ingested around 7.5g or more of paracetamol in the preceding 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.

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 periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits antipyretic activity.

Codeine is a centrally acting analgesic which produces its effect by its action at opioid-binding sites (m-receptors) within the CNS. It is a full agonist.

5.2. Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract with 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 usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

Codeine and its salts are absorbed from the gastro intestinal tract. Ingestion of codeine phosphate hemihydrate produces peak plasma codeine concentrations in about one hour. Codeine 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 administration by mouth or intravascular injection.

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

Sodium hydrogen carbonate, anhydrous sodium carbonate, anhydrous citric acid, sodium docusate, sorbitol, saccharin sodium, dimeticone, sodium benzoate, macrogol 6000, natural grapefruit flavour consisting of essential oil of grapefruit, concentrated citrus juices (lemon, orange and orange pulp, grapefruit), gentian infusion, cis-3-hexenol, ethyl 2-methylbutyrate, acacia gum, maltodextrin, butylated hydroxy anisole, water.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

Do not store above 25°C. Keep the container tightly closed.

6.5. Nature and contents of container

30 or 100 effervescent tablets in PP-tablet container with PE-stopper containing silica gel as desiccant

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Zanza Healthcare Ltd
Unit A1, Kingfisher
Business Park, Hawthorn Road
L20 6PF
Liverpool
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 15582/0022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/03/2006

10. DATE OF REVISION OF THE TEXT

07/03/2006

Patient Information Leaflet

Co-Codamol 30/500 mg Effervescent Tablets

What you should know about this medicine.

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

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and should not pass in on to others. It may harm them, even if their symptoms are the same as yours.

In this Leaflet:

The name of this medicine is Co-Codamol 30/500 mg Effervescent Tablets.

1. What is Co-Codamol 30/500 mg Effervescent Tablets ?

Each tablet contains 30 mg of the active ingredient Codeine Phosphate and 500 mg of the active ingredient Paracetamol, together with some other ingredients. These are included to aid the manufacture of the tablets and to make them soluble. These other ingredients are sodium hydrogen carbonate, anhydrous sodium carbonate, anhydrous citric acid, sodium docusate, sorbitol, saccharin sodium, dimeticone, sodium benzoate, macrogol, natural grapefruit flavour.

The sodium content of each tablet is approximately 410 mg, which amounts to 3.28 g of sodium daily at a maximum dose of 8 effervescent tablets per day. To be taken into consideration by patients on a sodium controlled diet.

Co-Codamol 30/500 mg Effervescent Tablets are white, bevelled, flat, round tablets with a break-line on one side.

Co-Codamol 30/500 mg Effervescent Tablets are available in packs of 30 or 100 effervescent tablets

The holder of the marketing authorisation for this medicine is Zanza Healthcare Ltd., Unit A1, Kingfisher Business Park, Hawthorne Road, Liverpool L20 6PF, Great Britain.

2. What is Co-Codamol 30/500 mg Effervescent Tablets used for?

Co-Codamol 30/500 mg Effervescent Tablets is a painkiller. It is recommended for the treatment of severe pain that is not alleviated by aspirin or paracetamol alone.

3. Before you take Co-Codamol 30/500 mg Effervescent Tablets

Do not take Co-Codamol 30/500 mg Effervescent Tablets if you:

- are allergic to codeine, paracetamol or any other of the ingredients
- experience severe asthmatic attacks or severe breathing problems
- have recently had a head injury
- have had recent gall bladder surgery or a similar operation
- have raised pressure in the brain
- take monoamine oxidase inhibitors (used to treat depression) or you have taken them in the last 14 days
- are an alcoholic.

Co-Codamol 30/500 mg Effervescent Tablets should not be given to children under 12 years of age.

Take special care with Co-Codamol 30/500 mg Effervescent Tablets (check with your doctor) if you:

- are pregnant or breast feeding
- have severe kidney or liver problems
- have prostate problems (e.g. difficulty passing water)
- a bowel disorder
- are elderly.

Pregnancy:
Ask your doctor or pharmacist for advice before taking any medicine.

Breast feeding:
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
Co-Codamol 30/500 mg Effervescent Tablets may cause drowsiness or dizziness. If affected you should not drive or operate machinery.

Important information about some of the ingredients of Co-Codamol 30/500 mg effervescent tablets:
Each Co-Codamol 30/500 mg effervescent tablets contains 410 mg of sodium which may be harmful to people on a low sodium diet.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Co-Codamol 30/500 mg Effervescent Tablets may change the effects of some medicines. Please check with your doctor or pharmacist if you are taking any of the following:

- chloramphenicol (an antibiotic)
- drugs which make you sleepy, including alcohol
- drugs used to thin the blood (e.g. warfarin)

In addition the following medicines may alter the effectiveness of Co-Codamol 30/500 mg Effervescent Tablets. However, Co-Codamol 30/500 mg Effervescent Tablets should not affect their action:

- metoclopramide/domperidone (used to treat nausea and vomiting)
- cholestyramine (used to treat high blood cholesterol (fat) levels)
- oral contraceptives ("the pill")

4. How to take Co-Codamol 30/500 mg Effervescent Tablets

Always take Co-Codamol 30/500 mg effervescent tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual dose of Co-Codamol 30/500 mg effervescent tablets 1 or 2 effervescent tablets not more often than every 4 hours. Do not take more than 8 effervescent tablets in any 24 hour period. Elderly may prescribed a lower dose.

Dissolve the effervescent tablets in half a tumblerful of water before taking.

Whilst taking Co-Codamol 30/500 mg effervescent tablets you should not take any other medicines which contain paracetamol. Do not exceed the recommended dose.

If you have the impression that the effect of Co-Codamol 30/500 mg effervescent tablets is too strong or too weak, talk to your doctor or pharmacist.

If you take more Co-Codamol 30/500 mg effervescent tablets you should:
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage. If you or someone else have taken an overdose tell your doctor or go to the nearest hospital casualty department immediately.

If you forget to take Co-Codamol 30/500 mg effervescent tablets:
Do not take a double dose to make up for forgotten individual doses.

5. Possible side effects

Like all medicines, Co-Codamol 30/500 mg Effervescent Tablets can have side effects.

If any of the following become troublesome you should tell your doctor: constipation, nausea (feeling sick), vomiting, dizziness, light-headedness, drowsiness, confusion and difficulty in passing water. If you suffer any unusual symptoms tell your doctor as soon as possible.

Rarely an allergic reaction can occur – this may involve a skin rash, swelling, itching or difficulty in breathing. If this occurs, tell your doctor immediately. There have been a few reports of low blood cell counts (platelets and white cells) associated with paracetamol-containing products but these were not necessarily due to paracetamol.

Chronic usage of Co-Codamol 30/500 mg Effervescent Tablets may lead to tolerance and dependence. If you have taken regular daily doses of Co-Codamol 30/500 mg Effervescent Tablets over a long period of time, you should not increase the dosage or suddenly stop your treatment without discussing this with your doctor.

If symptoms persist, consult your doctor.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. Storing Co-Codamol 30/500 mg Effervescent Tablets

Keep out of the reach and sight of children.
Do not use after expiry date stated on the label.

Store your medicine in the original container in order to protect from moisture.
Do not store above 25°C.
Keep the container tightly closed.

7. Further information

For any further information about this medicinal product, please contact the local representative of the marketing authorisation holder.

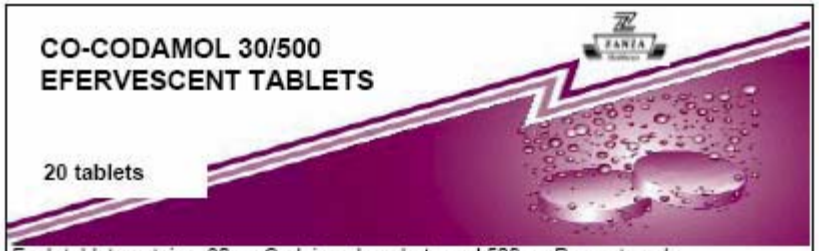
Zanza Healthcare Ltd., Unit A1
Kingfisher Business Park
Hawthorne Road
Liverpool L20 6PF - UK
Tel.: +44 151 922 4640
Fax.: +44 151 922 4161

This leaflet was last approved on June 2004

LABELLING


CO-CODAMOL 30/500mg
EFFERVESCENT TABLETS
BN: XXXX Use before: xx/xxxx
ZANZA
Healthcare
100 TABLETS
CO-CODAMOL 30/500
EFFERVESCENT TABLETS
Contains paracetamol.
Do not take with any other paracetamol containing products.
Immediate medical advice should be sought in the event of an overdose, even if you feel well.
For oral use.
To be taken dissolved in water in accordance with the directions of a physician.
See enclosed leaflet for further information.
Each tablet contains:
30mg Codeine phosphate
and 500mg Paracetamol
PL15582/0022
POM
Other ingredients include sorbitol and sodium salts. Sodium content approximately 410 mg/tablet. To be taken into consideration by patients on a controlled sodium diet.
Zanza Healthcare Ltd.
Unit A1
Kingfisher Business Park
Hawthorne Road
Liverpool
L20 6PF
100 TABLETS
CO-CODAMOL 30/500mg
EFFERVESCENT TABLETS
Codeine phosphate 30mg / Paracetamol 500mg
KEEP OUT OF REACH AND SIGHT OF CHILDREN
Do not store above 25°C
Keep the container tightly closed
BARC
ODE
506003
371112
5

CO-CODAMOL 30/500
EFERVESCENT TABLETS



20 tablets

Each tablet contains: 30mg Codeine phosphate and 500mg Paracetamol.
Other ingredients include sorbitol and sodium salts. Sodium content approximately 410 mg/tablet. To be taken into consideration by patients on a controlled sodium diet.
For oral use.
To be taken dissolved in water in accordance with the directions of a physician.
See enclosed leaflet for further information.
Do not store above 25°C. Keep container tightly closed.

POM

KEEP OUT OF REACH AND SIGHT OF CHILDREN
Zanza Healthcare Ltd, Unit A1, Kingfisher Business Park, Liverpool L20 6PF
PL 15582/0022

Contains paracetamol.
Do not take with any other paracetamol containing products.
Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Pantone 249