SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-dydramol 30/500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablet containing Paracetamol 500 mg, Dihydrocodeine Tartrate 30 mg

For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

An off-white capsule shaped tablet. The tablet is engraved on one side with "CODYD30" and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of severe pain where there is a higher analgesic requirement (higher than Co-dydramol 20/500 mg Tablets).

4.2 Posology and method of administration

Route of administration: Oral

Co-dydramol 30/500 mg tablets should, if possible, be taken during or after meals.

Children aged 12-15 years:

1 tablet every 4-6 hours

Do not take more than 4 tablets in any 24-hour period

Adults and children over 16 years of age:

One to two tablets every four to six hours. Maximum of eight tablets daily.

Children under 12 years:

Not recommended.

Elderly:

One to two tablets every four to six hours. Maximum of eight tablets daily.

Reduce dosage if renal or hepatic function is impaired.

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with dihydrocodeine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

4.3 Contraindications

Respiratory depression, obstructive airways disease, hypersensitivity to paracetamol, dihydrocodeine or other tablet constituents.

4.4 Special warnings and precautions for use

Co-dydramol tablets should be given with caution in patients with allergic disorders and should not be given during an attack of asthma.

Caution should be also observed if there is marked impairment of liver function, advanced kidney disease and in chronic alcoholics.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Do not exceed the recommended dose.

Patients should be advised not to take other paracetamol-containing products concurrently.

Dosage should be reduced in the elderly, in hypothyroidism and in chronic hepatic disease. An overdose can cause hepatic necrosis.

Dihydrocodeine should be used with caution in patients taking monoamine oxidase inhibitors and should be avoided in those patients with raised intracranial pressure or head injury.

Use with caution in patients with prostatic hypertrophy since dihydrocodeine may cause urinary retention.

The risk-benefit of continued use should be assessed regularly by the prescriber, and in particular the prescriber should take care to avoid any unnecessary increase in dosage especially where there is evidence of a previous history of drug dependence or abuse.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression.

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on- line, and past and present medical and psychiatric conditions. Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else. Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with dihydrocodeine.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

4.5 Interaction with other medicinal products and other forms of interaction

Additive CNS depression may occur with alcohol, and other CNS depressants such as anxiolytics, anti-depressants, hypnotics and anti-psychotics.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

The rate of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption of paracetamol may be reduced by cholestyramine.

The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy

At normal therapeutic doses there is epidemiological evidence of the safety of paracetamol in pregnancy, but patients should follow the advice of their doctor regarding its use. A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Dihydrocodeine has been used for many years without apparent ill effects. It should be used with caution in late pregnancy as it may cause respiratory depression in the neonate.

As with all medicines, use should be avoided during the first trimester.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding

Dihydrocodeine and paracetamol are excreted in breast milk in low concentrations. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Administration to nursing women is not recommended as dihydrocodeine may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

There are insufficient fertility data available to indicate whether paracetamol or dihydrocodeine has any effect on fertility.

4.7 Effects on ability to drive and use machines

Dihydrocodeine may cause drowsiness and, if affected, patients should not drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

The information below lists reported adverse reactions, using the following frequency classification:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Constipation, if it occurs, is readily treated with a mild laxative.

Abdominal pain.

Other side-effects of dihydrocodeine which may occur in a few patients are nausea, vomiting, headache, vertigo, giddiness, urinary retention, pruritus, sedation, dysphoria, hallucinations and allergic reactions including skin rashes.

Adverse effects of paracetamol are rare but hypersensitivity reactions including skin rash, blood dyscrasias, acute pancreatitis have been reported. Very rare cases of serious skin reactions have been reported.

Metabolism and nutrition disorders - frequency unknown: High anion gap metabolic acidosis. Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Dependence may occur. Regular prolonged use of dihydrocodeine is known to lead to addiction and tolerance. Frequency unknown: Drug dependence (see section 4.4). Symptoms of restlessness and irritability may result when treatment is then stopped.

General disorders and administration site conditions - uncommon: drug withdrawal syndrome

Prolonged use of a painkiller for headaches can make them worse. Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

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

Risk factors

If the patient

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

or

b) Regularly consumes ethanol in excess of recommended amounts.

or

c) Is likely to be glutathione depleted 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 with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the NPIS or a liver unit.

Dihydrocodeine

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms

Acute overdosage with dihydrocodeine can be manifested by somnolence progressing to stupor or coma, miotic pupils, rhabdomyolysis, non-cardiac pulmonary oedema, bradycardia, hypotension and respiratory depression or apnoea.

Management

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. In case of massive overdosage, administer naloxone intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response, or by an infusion. An infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event that IV access is not possible.

As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients. For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to dihydrocodeine overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on dihydrocodeine. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute

withdrawal syndrome.

Consider activated charcoal (50 g for adults, 10 - 15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

N02 BE71 Paracetamol combinations, with psycholeptics.

Paracetamol is an effective analgesic possessing a remarkably low level of side effects. Its broad clinical utility has been extensively reported, and it now largely replaces aspirin for routine use. Paracetamol is well tolerated; having a bland effect on

gastric mucosa, unlike aspirin, it neither exacerbates symptoms of peptic ulcer nor precipitates bleeding.

Dihydrocodeine tartrate has been widely used for a number of years as a powerful analgesic. In addition the compound exhibits well-defined anti-tussive activity.

Fortifying paracetamol with dihydrocodeine tartrate provides an effective combination of drugs for the treatment of severe pain.

5.2 Pharmacokinetic properties

Dihydrocodeine is well absorbed from gastrointestinal tract. Like other phenanthrene derivatives, dihydrocodeine is mainly metabolised in the liver with the resultant metabolites being excreted mainly in the urine. Metabolism of dihydrocodeine includes O-demethylation, N-demethylation and 6-keto-reduction.

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine as the glucuronide and sulphate conjugates.

5.3 Preclinical safety data

Paracetamol:

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Colloidal silica

Potassium sorbate

Povidone

Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 ºC. Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC blisters (Child resistant constructed from 250 micron PVC film lidded with 9 micron aluminium foil/35gsm glassine paper).

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Palla Pharma (UK) Holding Limited,
10 Norwich Street,
London,
EC4A 1BD

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