SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-dydramol 10/500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 500.00mg

Dihydrocodeine Tartrate 10.00mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet for oral use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-dydramol tablets are indicated for the relief of mild to moderate pain in musculoskeletal conditions (e.g. sciatica, osteoarthritis, chronic rheumatoid arthritis, sprains, strains etc.)

4.2 Posology and method of administration

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

Adults and children 16 years and over:

Analgesia:

One to two tablets every four to six hours. Do not take more than 8 tablets in 24 hours.

Children 12 – 15 years: One tablet every 4-6 hours when necessary to a maximum of 4 doses in any 24 hours.

Children under 12 years of age: ***Do not give to children under 12 years.***

Elderly:

The initial dose should be reduced in the elderly and subsequently adjusted according to response.

Hepatic impairment:

A reduction in dosage should be considered (see also 4.8 Undesirable Effects)

Renal impairment:

The dosage should be reduced in moderate to severe renal impairment (see also 4.8 Undesirable Effects)

For concomitant illnesses/conditions where dose reduction may be appropriate, see 4.4 Special Warnings and Precautions for Use.

Method of administration

For oral use.

4.3 Contraindications

Raised intercranial pressure or head injury (in addition to the risk of respiratory depression and increased intracranial pressure, may affect papillary and other responses vital for neurological assessment). Known hypersensitivity to paracetamol or dihydrocodeine tartrate, or to other opioid analgesics or to any of the excipients. Not to be given to children under twelve years. Severe hepatic dysfunction. Acute respiratory depression, obstructive airways disease. Acute alcoholism. Dihydrocodeine is also contra-indicated where there is a risk of paralytic ileus, or in

acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic associated colitis (e.g. pseudomembranous colitis) or diarrhoea caused by poisoning. Dihydrocodeine should not be given to comatose patients.

4.4 Special warnings and precautions for use

Co-dydramol should be given in reduced doses or with caution to patients with asthma and decreased respiratory reserve. Avoid use during an acute asthma attack (see 4.3 Contraindications).
Sensitivity to aspirin and other analgesics (see 4.8 Undesirable Effects).
Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with intravenous busulfan (see section 4.5 Interactions).
Co-dydramol should be given in reduced doses or with caution in elderly or debilitated patients (see 4.2 Posology & 4.8 Undesirable Effects) and in patients with adrenocortical insufficiency, prostatic hyperplasia, urethral stricture, hypotension, shock, inflammatory or obstructive bowel disorders, hypothyroidism, convulsive disorders or myasthenia gravis. It should be avoided or the dose reduced in patients with hepatic or renal impairment. Use with caution in patients with a history of drug abuse. Discontinuation should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms.

<u>Drug dependence, tolerance and potential for abuse</u>
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 to 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 tartrate.

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 respiratory rate or heart rate.

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 may resolve with a reduction of opioid dose.

Opioid analgesics should be avoided in patients with biliary tract disorders or used in conjunction with an antispasmodic.

Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions. If the use of codeine is considered essential then great care should be taken in patients taking MAOIs or within 14 days of stopping MAOIs (see section 4.5).

Alcohol should be avoided whilst under treatment with Co-dydramol.

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 dihydrocodeine (DHC) 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 DHC regularly for a long time can to lead to addiction.**

The hazards of overdose are greater in those with (non-cirrhotic) alcoholic liver disease. Not to be taken with any other paracetamol-containing products.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol should not be taken with other drugs that are potentially hepatotoxic or which may affect metabolism of paracetamol by the liver.

Alcohol: use should be avoided. The hypotensive, sedative and respiratory depressive effects of alcohol may be enhanced. Chronic alcohol abuse may increase the risk of hepatotoxicity with paracetamol overdosage.

Anaesthetics: concomitant administration of dihydrocodeine and anaesthetics may cause increased CNS depression and/or respiratory depression and/or hypotension.

Anti-arrhythmics: dihydrocodeine may delay the absorption of mexiletine. The analgesic activity of dihydrocodeine may be significantly impaired by quinidine which impairs codeine metabolism.

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

Cytotoxic drugs: Paracetamol possibly inhibits metabolism of intravenous busulfan (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol).

Antidepressants, anxiolytics, hypnotics: Opioids potentiate the effects of CNS depressants including anxiolytics (e.g. chlordiazepoxide, diazepam), hypnotics and tricyclic antidepressants.

MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with dihydrocodeine, it is possible that a similar interaction may occur and therefore the use of dihydrocodeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Antidiarrhoeal and antiperistaltic agents (such as loperamide and kaolin): concurrent use may increase the risk of severe constipation.

Antihistamines: concomitant administration of dihydrocodeine and antihistamines with sedative properties may cause increased CNS depression and/or respiratory depression and/or hypotension.

Antipsychotics: enhanced sedative and hypotensive effect.

Antivirals: The antiviral effect of interferon alpha may be enhanced with paracetamol; the combination has also been associated with increased liver enzyme levels.

Patients receiving zidovudine and paracetamol should be monitored for evidence of bone marrow or liver toxicity.

Chloramphenicol: Both an increase and decrease in plasma levels of chloramphenicol have been reported with the concurrent use of paracetamol.

Cholestyramine: The absorption of paracetamol is reduced by cholestyramine.

Domperidone and metoclopramide: dihydrocodeine antagonises the effect of cisapride, domperidone and metoclopramide on gastrointestinal activity. The absorption of paracetamol is accelerated by domperidone and metoclopramide.

Sodium oxybate: concomitant administration of dihydrocodeine and sodium oxybate may cause increased CNS depression and/or respiratory depression and/or hypotension.

Isoniazid: the liver toxicity of paracetamol may be increased by isoniazid. Patients taking isoniazid should limit their use of paracetamol.

Non-steroidal Anti-inflammatory drugs (NSAIDs): chronic concurrent high-dose administration of NSAIDs (other than aspirin) and paracetamol may increase the risk of nephrotoxicity.

Oral contraceptives: may reduce the analgesic effect of paracetamol by accelerating excretion.

Probenecid: Probenecid decreases paracetamol clearance. The clinical importance of this interaction is uncertain.

Ulcer-healing drugs: Cimetidine may inhibit the metabolism of dihydrocodeine resulting in increased plasma concentrations.

Diagnostic tests: Paracetamol can cause false blood glucose determinations

Interference with laboratory tests: Opioids may interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

4.6 Fertility, Pregnancy and lactation

A possible association with respiratory and cardiac malformations has been reported following first trimester exposure to codeine.

Dihydrocodeine may cause respiratory depression in the neonate. Opioid analgesics may cause withdrawal effects in neonates of dependent mothers and gastric stasis during labour, increasing the risk of inhalation pneumonia.

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

If opioid use is required for a prolonged period in a pregnancy 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.

Breast feeding

Administration to nursing women is not recommended as dihydrocodeine tartrate may be secreted in breast milk and may cause respiratory depression in the infant.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, 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. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

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

4.7 Effects on ability to drive and use machines

Dihydrocodeine produces sedation and may also cause changes in vision, including blurred or double vision. If affected, patients should not drive or operate machinery. The effects of alcohol are enhanced by opioid analgesics.

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 of 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

Regular prolonged use of dihydrocodeine 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.

Tolerance and some of the most common side effects – drowsiness, nausea, and vomiting, and confusion – generally develops with long term use.

Immune system disorders: maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate; fever, splenomegaly and lymphadenopathy also occurred.

Endocrine disorders: hyperglycaemia.

Metabolism and nutrition disorders: anorexia.

Psychiatric disorders: mental depression, hallucinations and nightmares, confusion, restlessness, mood changes, euphoria, dysphoria.

Frequency unknown: Drug dependence (see section 4.4)
General disorders and administration site conditions:
Uncommon: drug withdrawal syndrome

Nervous System disorders: dizziness, drowsiness, convulsions (especially in infants and children), headache (prolonged use of a painkiller for headaches can make them worse). Raised intracranial pressure may occur in some patients.

Eye disorders: blurred or double vision or other changes in vision. Miosis.

Ear and labyrinth disorders: vertigo

Cardiac disorders: tachycardia, palpitations and bradycardia.

Vascular disorders: postural hypotension, facial flushing. Large doses produce hypotension.

Respiratory, thoracic and mediastinal disorders: dyspnoea. Large doses produce respiratory depression.

Gastrointestinal disorders: dry mouth, nausea, vomiting, constipation, stomach cramps, pancreatitis.

Hepatobiliary disorders: Biliary spasm (may be associated with altered liver enzyme values).

Skin and subcutaneous tissue disorders: allergic reactions, such as skin rash, pruritus, urticaria, sweating and facial oedema.

Musculoskeletal and connective tissue disorders: Uncontrolled muscle movements. Muscle rigidity may occur after high doses.

Renal and urinary disorders: urinary retention, difficulty with micturition, ureteric spasm, dysuria. An antidiuretic effect may also occur with codeine.

Reproductive system and breast disorders: sexual dysfunction, erectile dysfunction, decreased potency. Decreased libido.

General disorders and administration site conditions: malaise, tiredness, hypothermia.

Adverse effects of paracetamol are rare but hypersensitivity including skin rash, urticaria or angioedema may occur. Anaphylactic reaction has been reported. Bronchospasm may be aggravated in patients sensitive to aspirin or other analgesics.
Gastrointestinal: Acute pancreatitis has occurred rarely after prolonged use of paracetamol.
Haematological: There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol. Leucopenia, neutropenia and pancytopenia have been reported in association with paracetamol.
Hepatic: Dose-related risk of hepatotoxicity in patients with significant hepatic impairment or after prolonged use of paracetamol

Renal: In patients with severe renal impairment prolonged use of high doses of paracetamol increases the risk of renal adverse events including renal colic and uraemia. Analgesic nephropathy, (characterised by renal papillary necrosis, chronic interstitial nephritis and eventually chronic renal failure), has been reported after prolonged use of paracetamol alone or in combination with NSAIDs, in patients without pre-existing renal impairment, although a causal association has not been established

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

Symptoms
The initial features are those of acute opioid overdosage, paracetamol hepatotoxicity may develop later.

Dihydrocodeine: The triad of coma, pinpoint pupils and respiratory depression is considered indicative of opioid overdosage with dilatation of the pupils occurring as hypoxia develops. Other opioid overdose symptoms include hypothermia, confusion, convulsions, severe dizziness, severe drowsiness, hypotension, nervousness or restlessness, hallucinations, slow heart beat, circulatory failure, slow or troubled breathing, severe weakness, convulsions, especially in infants and children. Rhabdomyolysis, progressing to renal failure, has been reported in overdosage with opioids.

Paracetamol: Symptoms of paracetamol overdose in the first 24 hours are sweating, 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, hypotension, cerebral oedema, coma and death. Prothrombin time may increase with deteriorating liver function. 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 arrythmias and pancreatitis have been reported.

Liver damage is possible in adults who have taken 10g or more of paracetamol. Chronic alcohol abuse and drugs that induce liver microsomal enzymes, such as phenobarbitone and isoniazid, can render paracetamol poisoning more severe.

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

Treatment

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 four 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.

In acute overdosage with respiratory depression or coma, the specific opioid antagonist naloxone is indicated, using one of the recommended dosage regimens. Patients should be observed closely.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol is an established analgesic of broad clinical utility.

Dihydrocodeine tartrate has been widely used as a powerful analgesic, and also has a well-defined antitussive action. The combination product therefore provides an effective treatment for mild to moderate pain, and also as an antipyretic.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the GI tract following oral dosage. Peak plasma levels are attained within 30 - 60 minutes and plasma half-life is about two hours.

Dihydrocodeine tartrate is well absorbed after oral administration, with peak plasma levels being attained within one and a half to two hours. The half-life being about three and a half-hours.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber, which are additional to those included in other sections.

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

Pregelatinised starch
Povidone K30
Magnesium stearate
Purified water

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months for tablets in polypropylene/polyethylene tablet containers.

24 months for tablets in blister strips.

6.4 Special precautions for storage

Store below 25°C.

Blister strips: Keep the blisters in the outer carton in order to protect from light.

Polypropylene/polyethylene tablet containers: store in the original container.

6.5 Nature and contents of container

Polypropylene or polyethylene containers containing 500,1000 or 5000 tablets.

30 or 100 tablets in blister strips consisting of a 35gsm/9µ soft tempered aluminium foil lid and 250µ PVC film base in cartons.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Austin McNeil Ltd.,
772 Fulham Road, London,
SW6 5SJ, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 53797/0061

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

28/04/2025