# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Co-Dydramol Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 10mg of Dihydrocodeine tartrate BP and 500mg Paracetamol BP

## 3 PHARMACEUTICAL FORM

White, flat circular plain tablets with a bevel edge and breakline.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

1. An analgesic
2. An antitussive

### 4.2 Posology and method of administration

Co-Dydramol tablets should be taken if possible, during or after meals.

Treatment goals and discontinuation

Before initiating treatment with Co-Dydramol, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4)

**Adult Dosage**

As an analgesic:

Adults and children over 15 years:

1 tablet every four hours. This may if necessary be increased to 2 tablets four times daily.
For the age 12 – 15 years one tablet every 4-6 hours when necessary to a maximum of 4 doses in 24 hours.

As an antitussive:
Adults and children over 15 years:
1 tablet every four hours.
For the age 12 – 15 years one tablet every 4-6 hours when necessary to a maximum of 4 doses in 24 hours.

Not recommended for children under 12 years.
Dosage should be reduced in the elderly.
Not more than 8 tablets in 24 hours.

Duration of treatment
The duration of treatment should be as short as possible, and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

**Route of administration**

Oral.

## 4.3 Contraindications

Respiratory depression, obstructive airway disease, allergic disorders or during an attack of asthma. Hypersensitivity to Paracetamol and /or other constituents.

## 4.4 Special warnings and precautions for use

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Co-Dydramol. Repeated use of Co-Dydramol can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Co-Dydramol may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Co-Dydramol tablets and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-

active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Hepatobiliary disorders

Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine/paracetamol has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Risks from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

The risk-benefit of continued use should be assessed regularly by the prescriber. Use with caution in impaired liver function or renal disease. Reduce dosage in hypothyroidism and in chronic hepatic disease. May cause constipation, nausea, headache, vertigo & giddiness in some patients. Care is advised in the administration if paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with (non-cirrhotic) alcoholic liver disease. Do not exceed the recommended dose.

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.

Drug withdrawal syndrome

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 characteried by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may 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.

## 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 use of paracetamol with increased risk of bleeding: occasional doses have no significant effect.

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)

Concomitant use of Co-Dydramol with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

## 4.6 Fertility, Pregnancy and lactation

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.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data on paracetamol do not contraindicate breast-feeding.

## 4.7 Effects on ability to drive and use machines

None stated

## 4.8 Undesirable effects

Regular prolonged use of dihydrocodeine is known to lead to addiction, and symptoms of restlessness, abdominal/stomach pain and irritability may result when treatment is then stopped. Prolonged use of a painkiller for headaches can make them worse. 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 casually related to paracetamol.

Gastrointestinal disorders
Not known: pancreatitis

Hepatobiliary disorders
Not known: sphincter of Oddi dysfunction

Metabolism and nutrition disorders
"High anion gap metabolic acidosis'' with frequency ''Not known'' (cannot be estimated from the available data)

Description of selected adverse reactions

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.

Drug dependence
Repeated use of Co-Dydramol can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

## 4.9 Overdose

**Paracetamol**

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. 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.

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. Management of

patients who present serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Symptoms of paracetamol overdose 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, gastroinstestinal bleeding, coma 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.

Liver damage is likely 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.

**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 the 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 minutes 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 an adult presents within 1 hour of ingestion of more than 420mg or a child more than 3mg/kg.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Peak levels of plasma dihydrocodeine concentration are attained in an hour, following ingestion. Plasma half-life has been reported to be between 3-4 hours after oral ingestion. Dihydrocodeine is metabolised in the liver by O- and N- demethylation. Dihydrocodeine and its metabolites are excreted entirely by the kidneys mainly as conjugates with glucuronic acid.

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentration occurring 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and the sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half - life varies from 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 small amounts by mixed-function oxidases in the liver and which is usually de-toxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and may cause liver damage.

### 5.2 Pharmacokinetic properties

The pharmacokinetics of dihydrocodeine may be similar to codeine: they differ between subjects with normal renal function and those with chronic renal failure treated with haemodialysis. Dihydrocodiene is well absorbed from the gastrointestinal tract following oral administration. Plasma half-life has been reported to between 3-4 hours after oral ingestion.

### 5.3 Preclinical safety data

Not applicable

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Maize Starch
Povidone (K= 29/32)
Sodium Starch Glycollate
Stearic Acid
Colloidal Silicone Dioxide
Talc

### 6.2 Incompatibilities

None Stated

### 6.3 Shelf life

12 Months

### 6.4 Special precautions for storage

Store in a cool dry place below 25°C. Protect from light.

### 6.5 Nature and contents of container

Securitainers in pack sizes if 16, 25, 30, 32, 50, 100, 250, 500 and 1000.

PVC blisters of 16, 32 and 100.

### 6.6 Special precautions for disposal

None stated.

## 7 MARKETING AUTHORISATION HOLDER

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## 8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0159

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26th September 1994

## 10 DATE OF REVISION OF THE TEXT

15/04/2026