Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Codipar 15mg/500mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Codeine Phosphate hemihydrate 15mg and Paracetamol 500mg,
Excipient(s) with known effect:

Each tablet also contains 389mg of sorbitol and 379 mg of sodium.
For the full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablet
Bevelled, flat, round, white tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of mild to severe acute pain

Codeine is indicated in patients older than 12 years of agefor the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Posology
Adults: The usual dose is two tablets every six hours as required. The total daily dose should not exceed 4 g paracetamol (8 tablets in a day).

Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. The total daily dose should not exceed 120mg codeine (8 tablets in a day)
The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Older people: As for adults, however a reduced dose may be required (see section 4.4)

Paediatric population:
Children aged 16 and over:
Two tablets to be taken every six hours as required, up to a maximum of eight tablets in any 24-hour period.

Children aged 12 to 15 years:
One tablet to be taken every six hours as required, up to a maximum of four tablets in any 24-hour period.

Children aged less than 12 years:
Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Method of administration: Oral

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

4.3 Contraindications

Hypersensitivity to either paracetamol or codeine, or to any of the excipients listed in section 6.1.

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.

Codipar is also contraindicated in severe liver disease and severe renal impairment. The hazards of overdose could be greater in those with alcoholic liver disease.

In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life threatening adverse reactions (see section 4.4).

In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers
In women during breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Care should be observed in administering the product to any patient whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy / urethral stricture and those with inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated, since side effects are more frequent and may lead to intolerance of the product with regular, long-term use.

Codeine at high doses has the same disadvantages as morphine, including respiratory depression. Drug dependence of the morphine type can be produced by codeine, and the potential for drug abuse with codeine must be considered. Codeine may impair mental or physical abilities required in the performance of potentially hazardous tasks.

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

Concomitant use of Codipar Effervescent Tablets and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Codipar Effervescent Tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms such as restlessness and irritability, once the drug is stopped.

Care should be taken in patients with liver and kidney disease with suitable dose reductions as appropriate.

Prolonged use except on the doctor's advice may be harmful.

This product should be used only when clearly necessary.

CYP2D6 metabolism
Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.
General symptoms of opioid toxicity include confusion, shallow breathing, small pupils, nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Estimates of prevalence of ultra-rapid metabolizer in different populations are summarized below:

Population	Prevalence %

African Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

Immediate medical advice should be sought in the event of overdosage, even if the patient feels well, because of the risk of irreversible liver damage.

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

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

Patients must be advised not to take other products containing paracetamol or opiate derivatives when taking Codipar, and to consult their doctor if symptoms persist.

The cough suppressant effect of codeine may be undesirable in patients with some respiratory conditions.

As the effervescent tablet contains 389mg of sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicine contains 379 mg sodium in each tablet. This should be taken into consideration by patients on a controlled sodium (salt) diet.

4.5 Interaction with other medicinal products and other forms of interactions

The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated by codeine.

The CNS depressant action of Codipar may be enhanced by coadministration with any other drug which has a CNS depressant effect (e.g. anxiolytics, hypnotics, antidepressants, antipsychotics and alcohol). Concomitant use of any drug with a CNS depressant action should be avoided. If combined therapy is necessary, the dose of one or both agents should be reduced.

Concomitant administration of Codipar and MAOIs or tricyclic antidepressants may increase the effect of either the antidepressant or codeine.

Concomitant administration of codeine and anticholinergics may cause paralytic ileus.
Concomitant administration of codeine with an anti-diarrhoeal agent increases the risk of severe constipation, and coadministration with an antimuscarinic drug may cause urinary retention.

The absorption of paracetamol may be enhanced by metoclopramide or domperidone, and absorption may be reduced by cholestyramine.
The metabolism of paracetamol is increased in patients taking enzyme-inducing antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone).
Isolated reports describe unexpected hepatotoxicity in patients taking phenobarbital, phenytoin, or carbamazepine after taking paracetamol.

The anticoagulant effect of warfarin and other coumarins may be increased by long term regular daily use of paracetamol, with increased risk of bleeding. Occasional doses of paracetamol do not have a significant effect on these anticoagulants.

Dependence of codeine hypoalgesia on morphine formation via CYP2D6 makes this effect liable to interaction with drugs that are inhibitors of CYP2D6. Examples of potent inhibitors of CYP2D6 are quinidine, some selective serotonin reuptake inhibitors, some neuroleptics and ritornavir.

Codeine may delay the absorption of mexilitine.

4.6 Fertility, pregnancy and lactation

Pregnancy: On the basis of published literature (Danish National Birth Cohort), paracetamol use during any time of pregnancy was associated with a small but statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months.

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.

Use of codeine during pregnancy may lead to withdrawal symptoms in neonates, and use during labour may cause neonatal respiratory depression.

Codipar is then not recommended during pregnancy.

Breast-feeding:
The use of codeine is contraindicated during breastfeeding (see section 4.3).
At normal therapeutic doses codeine and its active metabolitesmay be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

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

Fertility:
There are no data on the effects of this medicine on human fertility. Fertility was unaffected following paracetamol or codeine treatment in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if Codipar causes dizziness or sedation. Codeine may cause visual disturbances.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. 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 may be an offence to drive while under the influence of this medicine

4.8 Undesirable effects

Reported adverse reactions seem more prominent in ambulatory than non-ambulatory patients and some of these effects may be alleviated if the patient lies down.

The information below lists reported adverse reactions, ranked 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).

System organ class	Frequency	Adverse effects
Blood and lymphatic system disorders	Rare	Blood disorder, Thrombocytopenia, Agranulocytosis
Immune system disorder	Rare Not known	Hypersensitivity (including skin rash)[a] Anaphylactic reaction, Anaphylactic shock, Angioedema
Psychiatric disorders	Common Not known	Dysphoria, Euphoria Drug dependence[d], Restlessness[d], Irritability[d]
Nervous system disorders	Common	Dizziness, Light-headedness,

	Not known	Sedation, Confusion, drowsiness,
Eye Disorder	Not known	Miosis
Respiratory, thoracic and mediastinal disorders	Common Not known	Shortness of breath Respiratory depression[b]
Gastrointestinal disorders	Common Not known	Nausea & vomiting, Constipation, Abdominal pain, Pancreatitis,
Hepatobiliary disorders	Not known	Liver damage[c]
Skin and subcutaneous tissue disorders	Common	Pruritus, Rash, Urticaria,
Renal and urinary disorders	Not known	Urinary retention

a. Rarely hypersensitivity including skin rash may occur with paracetamol use.
b. Codeine can cause respiratory depression particularly in overdosage and in patients with compromised respiratory function (see Section 4.9).
c. Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.
d. Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

Very rare cases of serious skin reactions have been reported.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Codeine

Symptoms
Large doses of codeine produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur from respiratory failure. Blood concentrations of codeine ranged from 1.4 to 5.6 mg/l in eight adults whose deaths were attributed primarily to codeine overdosage.

Management
Primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway and the institution of controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Opioid antagonists may be employed. Gastric lavage should be considered. Patients should remain under observation, as per hospital guidelines and on a case per case basis.

Paracetamol

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. Hyperglycaemia has been reported. 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.

Because of its ready availability, paracetamol is often taken in overdosage. Toxicity is likely if more than 150 mg/kg of paracetamol is ingested. The major complication is acute hepatic necrosis, although without treatment fewer than 10% of unselected patients are at risk of severe liver damage (plasma aminotransferase > 1000 mg/l). About 1% develop fulminant

hepatic failure which is usually fatal. Renal failure from acute tubular necrosis is a further uncommon complication which may develop in the absence of hepatic failure. There are no specific early manifestations of severe paracetamol poisoning. Consciousness is not impaired except in the occasional unusually severely poisoned patient with metabolic acidosis, and maximum abnormality of liver function tests is delayed for at least 3 days.

Emergency estimation of the plasma paracetamol concentration is therefore necessary to determine the severity of intoxication and the need for specific therapy with N-acetylcysteine (NAC).

Management
Patients who have ingested more than 150 mg/kg should have gastric lavage performed if they present within an hour of ingestion. Activated charcoal may also be given. A plasma paracetamol level will indicate the likelihood of a patient developing high ALT/AST activities (i.e.> 1,000 i.u. /L) and must be measured at least 4 hours after ingestion. Plasma levels measured less than 4 hours' post-ingestion cannot be interpreted. Patients with a plasma level above the treatment line require N-acetylcysteine (NAC). A paracetamol normogram should be employed to determine treatment levels.

Patients who present to an Accident and Emergency Department more than 8 hours after ingesting a paracetamol overdose are at greater risk of developing hepatic damage. In cases of severe poisoning, hepatic failure may progress to encephalopathy, coma and death.

Blood should be taken for a plasma level, but the NAC infusion should be started as soon as possible if more than 150 mg/kg was taken. The NAC infusion should not be delayed while awaiting the result of the plasma paracetamol level. Administration of the antidote should be stopped if the plasma level is subsequently found to be below the treatment line. General supportive measures must be available.

At the end of the NAC infusion, blood should be taken to check the INR and creatinine concentration. If the investigations are abnormal, a further infusion of NAC (at 16-hour dose), to be continued until recovery or death, should be considered.

In the range of concentrations associated with overdosage, paracetamol may give a false positive result for plasma salicylate in tests based on the direct colour reaction with ferric ions. In the same circumstances it may induce spuriously high results for blood dextrose estimated with the YSI and Yellow Springs Model 23AM dextrose analyzers. Conversely, it may cause falsely low results for dextrose when the dextrose peroxidase/dextrose-6-phosphate dehydrogenase method is used.

Liver damage following overdosage is relatively uncommon in young children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol
Pharmacotherapeutic group: paracetamol, combinations excl. psycholeptics
ATC Code: NO2B E51

Mechanism of action:
Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Paracetamol is a weak, reversible, isoform-nonspecific cyclooxygenase inhibitor at dosages of 1 g daily. The inhibitory effect of paracetamol on cyclooxygenase-1 is limited, and the drug does not inhibit platelet function. Animal studies have indicated that paracetamol strongly inhibits prostaglandin synthetase in the brain (which may account for its antipyretic and analgesic effects) but that it has little effect on peripheral tissue prostaglandins (which are involved in inflammatory reactions).

Codeine
Pharmacotherapeutic group: codeine, combinations excl. psycholeptics
ATC code: N02AA59

Mechanism of action:

Codeine is a centrally acting analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has an exceptionally low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. However, its antitussive actions may involve distinct receptors that bind codeine itself.

The conversion of codeine to morphine is effected by the CYP2D6. Well-characterised genetic polymorphism in CYP2D6 lead to the inability to convert codeine to morphine, thus making codeine ineffective as an analgesic for about 10% of the Caucasian population.

Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain. However, data in chronic pain, cancer pain and neuropathic pain are lacking.

5.2 Pharmacokinetic properties

Paracetamol:

Absorption:
Paracetamol is rapidly and completely absorbed after oral administration, with peak plasma concentrations occurring between 15 min and 2 h after ingestion.

Distribution:
Paracetamol is distributed throughout most body tissues, with an apparent volume of distribution of approximately 1 L/kg of body weight. Concentrations in whole blood are up to 20% higher and in breast milk about 20% lower. Paracetamol crosses the placenta.

Biotransformation:
Paracetamol is extensively metabolised in the liver and the total body clearance is about 5 ml/min/1/kg.

Elimination:
Some 2-5% of a therapeutic dose of paracetamol is excreted unchanged in the urine.

Codeine:

Absorption:
Codeine is absorbed rapidly following oral administration; peak plasma concentrations occur in about 1 h and the plasma half-life is about 3.5 h.

Distribution:
The volume of distribution is approximately 3.6 l/kg. The total body clearance of codeine is approximately 0.85 l/min. Codeine crosses the placentaand is present in the milk of lactating mothers.

Biotransformation:
Codeine is metabolised in the liver by *O*-demethylation to form morphine (codeine is in fact a pro-drug to morphine), and other metabolites.

Elimination:
After an oral dose, about 86% is excreted in the urine in 24 h as free drug and metabolites, mostly in the form of metabolites. Some of a dose of codeine is excreted in the bile and trace amounts are found in the faeces. Unchanged drug accounts for 6-8% of the dose in urine in 24 h.

The bioavailabilities of paracetamol and codeine, when given as the combination, are similar to those when they are given separately.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.
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

Sodium Hydrogen carbonate
Sodium carbonate anhydrous
Citric acid anhydrous
Sorbitol Neosorb P60 W
Povidone K30
Sodium Saccharin
Macrogol 6000
Grapefruit flavour

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25ºC

6.5 Nature and contents of container

Strips of Aluminium / polyethylene foils
Each strip contains 4 tablets individually packed in cardboard containers.of 100 tablets.

6.6 Special precautions for disposal and other handling

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.
No special requirements for disposal .

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/023/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th October 2010
Date of last renewal: 11th August 2015

10 DATE OF REVISION OF THE TEXT

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