Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Codipar 15 mg/ 500 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Paracetamol 500mg, and Codeine Phosphate Hemihydrate 15mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard
Codipar Capsules are size 0 hard gelatin capsules consisting of a red cap and white body, filled with a homogenous white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of mild to severe acute pain in adults.

Codipar is indicated in patients older than 12 years of age for 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 2 capsules every 6 hours as required.
The total daily dose should not exceed 4 g paracetamol (8 capsules 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 120 mg codeine (8 capsules 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.

Elderly
As for adults, however a reduced dose may be required (see section 4.4)
Experience has indicated that normal adult paracetamol dosage is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

Renal impairment:
It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:
Adults:

Glomerular filtration rate	Dose
10-50 ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

Hepatic impairment:
In patients with hepatic impairment or Gilbert's Syndrome, the paracetamol dose should be reduced or the dosing interval prolonged.

The daily dose of paracetamol should not exceed 2g/day unless directed by a physician.

The maximum daily dose of paracetamol should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following situations, unless directed by a physician:
- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Paediatric population:
Children aged 16 years and over:
2 capsules to be taken every 6 hours as required, up to a maximum of 8 capsules in any 24-hour period.

Children aged 12 years to 15 years: 1 capsule every 6 hours with a maximum of 4 capsules in 24 hours 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

Treatment goals and discontinuation
Before initiating treatment with Codipar, 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).

Duration of treatment
Codipar should not be used longer than necessary.

4.3 Contraindications

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

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 Codipar. Repeated use of Codipar 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 Codipar 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 Codipar 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.

Sleep-related breathing disorders
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.

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 has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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.

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 ormyasthenia gravis. 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. Codeine may impair mental or physical abilities required in the performance of potentially hazardous tasks.

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):
- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR≤50ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.
If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.
Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

Risk from concomitant use of sedative medicines (such as benzodiazepines or related drugs) and gabapentinoids:

Concomitant use of Codipar Capsules and sedative medicines (such as benzodiazepines or related drugs) and gabapentinoids (gabapentin and pregabalin) may result in profound sedation, respiratory depression, hypotension, coma or death. Because of these risks, concomitant prescribing with these medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Codipar Capsules concomitantly with sedative medicines or gabapentinoids, 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.

<u>Paediatric population</u>

Post-operative use in children
There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultrarapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function
Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Information on Sodium Content
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 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.
Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

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 is speeded by metoclopramide or domperidone, and absorption is 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 ritonavir.

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 metabolitemay 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 metabolites 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.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.
Paracetamol is excreted in breast milk but not in a clinically significant amount.

Fertility
There is no information available concerning the effect of this medicinal product on fertility.

4.7 Effects on ability to drive and use machines

Codipar has minor influence on the ability to drive and use machines. Codipar may cause dizziness, or sedation and visual disturbances.

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[b], Thrombocytopenia[b], Agranulocytosis[b]
Immune system disorders	Rare Not known	Hypersensitivity[c] Anaphylactic reaction, Anaphylactic shock, Angioedema
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis[g]
Psychiatric disorders	Common Not known	Dysphoria , Euphoria Drug dependence[d] , Restlessness[d] ,Irritability[d]
Nervous system disorders	Common Not known	Dizziness, Light headedness, Sedation, Headache Brain Oedema, Confusion
Eye disorder	Not known	Miosis
Respiratory, thoracic and mediastinal disorders	Common Not known	Shortness of breath Respiratory depression[f]

Gastrointestinal disorders	Common Not known	Nausea, Vomiting, Constipation, Abdominal pain Pancreatitis
Hepatobiliary disorders	Not known	Liver damage[e], Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Common Very rare Not known	Pruritus , Rash, Urticaria Toxic epidermal necrolysis(TEN)[a], Stevens Johnson Syndrome[a], Acute generalised exanthematous pustulosis[a] Drug Eruption
Renal and urinary disorder	Not known	Urinary retention

1. Very rare cases of serious skin reactions have been reported.
2. In clinical use of paracetamol-containing products.
3. Rarely hypersensitivity including skin rash may occur with paracetamol use. _
4. Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.
5. Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.
6. Codeine can cause respiratory depression particularly in overdosage and in patients with compromised respiratory function (see Section 4.9).
7. 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 Codipar 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).

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 Website: www.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

Because of its ready availability, paracetamol is often taken in overdosage. Toxicity is likely if more than 150 mg/kg of paracetamol is ingested. Paracetamol overdose can result in liver damage which may be fatal. Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue. 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.

Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors include;

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Hyperglycemia associated with overdose has been reported.

Management

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).

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

Pharmacotherapeutic group: Paracetamol, combinations excl. Psycholeptics, ATC Code: N02B 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).

Pharmacotherapeutic group: Codeine, combinations excl. psycholeptics, ATC code: N02AA59
Mechanism of action:

Codeine is a centrally acting weak 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 7% of the Caucasian population.

The fixed combination of paracetamol and codeine 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 placenta and 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

There are no findings of relevance to the prescriber other than those already mentioned elsewhere in the SPC.
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

Capsule Contents:
Maize Starch
Sodium laurilsulfate
Croscarmellose sodium
Talc
Magnesium Stearate

Capsule Shell:
Gelatin
Titanium dioxide (E171)
Erythrosine (E127)
Red Iron Oxide (E172)

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

Blister strips of PVDC coated Aluminium / polypropylene foils
Blister strips of 10.
In pack size of 100 capsules.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Unit 17
Northwood House
Northwood Crescent
Northwood
Dublin 9
D09 V504
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/023/002

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