SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Solpadeine Max Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg and Codeine phosphate hemihydrate

12.8 mg.

Excipients with known affect:

Lactose monohydrate 5.9 mg per tablet

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Red film coated, capsule shaped tablets plain on both the sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine 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.

Solpadeine Max Tablets are recommended for the relief of migraine, headache, dental pain, period pain, backache, arthritic & rheumatic pain, strains & sprains and sciatica.

4.2 Posology and method of administration

Posology

Adults
Two tablets every 4-6 hours, up to 4 times a day. The minimum dosing interval is 4 hours. No more than 4 doses (8 tablets) in 24-hours.

Paediatric population:
Adolescents aged 16-18 years:
1-2 tablets every 6 hours up to 4 times a day. The minimum dosing interval is 6 hours. No more than 4 doses (8 tablets) should be given in 24 hours.

Adolescents aged 12 – 15 years:
1 tablet every 6 hours up to 4 times a day. The minimum dosing interval is 6 hours. No more than 4 doses (4 tablets) should be given in 24 hours.

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).

Elderly patients:
Elderly patients, especially those who are frail or immobile, may require a reduced dose or frequency of dosing.

Renal impairment:
Patients who have been diagnosed with kidney impairment must seek medical advice before taking this medication. It is recommended, when giving paracetamol to patients with renal failure, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours. The restrictions related to the use of paracetamol products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

Hepatic impairment:
Patients who have been diagnosed with hepatic impairment or Gilbert's Syndrome must seek medical advice before taking this medication. The restrictions related to the use of paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

A reduced maximum daily dose should be considered in patients who are underweight (for adults, those under 50kg) (see section 4.4 and 4.9)

Method of administration

For oral administration only.

Do not exceed the recommended daily dosage or the specified number of

doses because of the risk of liver damage (see section 4.4 and 4.9).
Minimum dosing interval: 4 hours for adults and 6 hours for adolescents.

Treatment goals and discontinuation

Before initiating treatment with the product, treatment duration and treatment goals 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

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 healthcare professional.

If pain or fever persists for more than 3 days or gets worse, or if any other symptoms occur, treatment should be discontinued and a physician consulted

4. CLINICAL PARTICULARS

4.3 Contraindications

Hypersensitivity to paracetamol, codeine, opioid analgesics or any of the other constituents.

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 women who are pregnant or breastfeeding (see section 4.6)

In respiratory depression, chronic constipation.

In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

Deleted: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.¶

Deleted: during

4.4 Special warnings and precautions for use

Care is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Paracetamol should be administered only with particular caution under the following circumstances:

- Hepatocellular insufficiency
- Chronic alcoholism
- Renal failure (GFR $\leq$ 50 ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphatase dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- The elderly, adults and adolescents weighing less than 50 kg

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, hypothyroidism and those with inflammatory or obstructive bowel disorders, Addison's disease or myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Precaution should be observed in patients with asthma who are sensitive to acetylsalicylic acid since mild bronchospasms are reported in association with paracetamol (cross reaction).

Do not exceed the stated dose.
Patients should be advised not to take other paracetamol or codeine-containing products concurrently. Immediate medical advice should be sought in the event of overdosage even if the patient feels well because the risk of irreversible liver damage (see section 4.9).

If symptoms persist for more than 3 days or get worse, or if any other symptoms occur, treatment should be discontinued, and a physician consulted.

Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.

Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients.

Patients taking, or who have taken, monoamine oxidase inhibitors (MAOIs) within the preceding two weeks (see section 4.5) should not take this product.

Hepatotoxicity has been reported due to prolonged use of paracetamol at higher than recommended doses. This risk is increased with the use of codeine/paracetamol-combinations as patients may become dependent on the codeine component (see warning above, section 4.8 and section 4.9).

Codeine, as with other opioids should be used with caution in patients with hypotension, hypothyroidism, head injury or raised intracranial pressure.

CYP2D6 metabolism

Codeine is metabolized 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 extensive or ultra-rapid metabolizer 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, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. 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 metabolisers 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%

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 ultra-rapid or extensive metabolisers in their ability to metabolize 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.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per 2 tablets, that is to say essentially 'sodium-free'.

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 Solpadeine Max Tablets. Repeated use of Solpadeine Max Tablets 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 Solpadeine Max Tablets 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).
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.

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.

Sleep-related breathing disorders including central sleep apnoea:
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.

Drug withdrawal syndrome
Addiction can cause drug withdrawal syndrome upon abrupt cessation of therapy or dose reduction.

The opioid drug withdrawal syndrome is characterized 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.

Risk from concomitant use of medicines with sedative effects
Concomitant use of Solpadeine Max Tablets and medicines with sedative effects such as benzodiazepines or related drugs (such as pregabalin and gabapentin) may result in sedation, respiratory depression, coma and increased risk for opioid-related death. Because of these risks, concomitant administration of these medicines with sedative effects should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Solpadeine Max Tablets concomitantly with medicines with sedative effects, 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).

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. Cholestyramine should not be administered within one hour of taking paracetamol.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Paracetamol is metabolized in the liver and can therefore interact with

other medicines that follow the same pathway or may inhibit or induce this route (e.g. barbiturates, such as phenobarbitone, tricyclic antidepressants, alcohol, carbamazepine, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes), causing hepatotoxicity, particularly in overdose (see section 4.9).

In case of concomitant treatment with probenecid, the dose of paracetamol should be reduced because probenecid reduces the clearance of paracetamol by 50% since it prevents the conjugation of paracetamol with glucuronic acid.

There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics, but its validity has been criticized and evidence of a clinically relevant interaction appears to be lacking. Although no routine monitoring is needed, it is important to bear in mind this potential interaction when these two medications are concomitantly administered, especially in malnourished patients.

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).

Codeine

Codeine may antagonize the effects of metoclopramide and domperidone on gastrointestinal motility.

Codeine potentiates the central depressive effects of central nervous system depressants including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

Opioid analgesics should be given with care to patients receiving monoamine oxidase inhibitors. The effect of CNS depressants (including alcohol) may be potentiated by codeine; these interactions are unlikely to be significant at the dosage involved.

MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.
Opiate analgesics may interact with monoamine oxidase inhibitors (MAOIs) and result in serotonin syndrome. It is recommended that the product should not be taken concurrently or within two weeks of stopping treatment with a MAOI.

Medicines with sedative effects:
The concomitant use of opioids with medicines with sedative effects such

as benzodiazepines or related drugs, gabapentinoids (gabapentin and pregabalin) may result in profound sedation, respiratory depression, hypotension, coma and opioid-related death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

4. CLINICAL PARTICULARS

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Solpadeine Max Tablets should not be used during pregnancy. This includes maternal use during labor because of the potential for respiratory depression in the neonate.

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

The patient should be advised of the risk of neonatal opioid withdrawal syndrome, and it should be ensured that appropriate treatment will be available.

Paracetamol
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.

Lactation

Solpadeine Max Tablets should not be used during breastfeeding (see section 4.3), as codeine may be secreted in breast milk and may cause respiratory depression in the infant. At normal therapeutic doses codeine and its active metabolite may 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 metabolizer of CYP2D6, higher levels of the active metabolite, morphine, 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.

Fertility

There are no data available regarding the influence of Solpadeine Max Tablets on fertility.

4.7. Effects on Ability to Drive and Use Machines

Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When taking 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 taken to treat a medical or dental problem and
  - You have taken it according to the information provided with the medicine and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system. The following convention has been utilized for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, 363 <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Paracetamol

Body System	**Undesirable effect**	**Frequency**
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis	Not known
Immune system disorders	Anaphylaxis	Not known
	Allergies (not including angioedema)	Rare
Metabolism and nutrition disorders	High anion gap metabolic acidosis	Not known
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	Not known
Hepatobiliary disorders	Hepatic dysfunction	Not known
	Cutaneous hypersensitivity reactions including skin rashes, pruritus, sweating, purpura, urticaria and angioedema	Very rare

Skin and subcutaneous tissue disorders	Very rare cases of serious skin reactions have been reported Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced dermatitis, acute generalized exanthematous pustulosis (AGEP)	Very rare
Renal and urinary disorders	Sterile pyuria (cloudy urine)	Very rare

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.

*** There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.**

Codeine
Adverse reactions identified during post-marketing use are listed below by MedDRA system organ class. The frequency of these reactions is not known.

Body System	**Undesirable effect**	**Frequency**
Psychiatric disorders	Drug dependency can occur after prolonged use of codeine (see section 4.4)	Not known
Gastrointestinal disorder	Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy	Not known
Nervous system disorder	Dizziness, Hyperalgesia, worsening of headache with prolonged use, Drowsiness.	Not known
General disorders and administration	Drug withdrawal syndrome	Uncommon
Renal and urinary disorders	Difficulty with micturition	Not known
Skin and subcutaneous tissue disorder	Pruritus, sweating	Not known
Hepatobiliary disorders	Sphincter of Oddi dysfunction	Not known

Drug dependence
Repeated use of Solpadeine Max Tablets 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 authorization 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

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Codeine

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. 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.

Prolonged use at higher than recommended doses may result in severe hepatotoxicity (see section 4.4).

Symptoms

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pinpoint in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life, so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

Paracetamol

Paracetamol overdose can result in liver damage which can be fatal. Liver damage is possible 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. 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.

Symptoms

Symptoms of paracetamol overdose generally appear in the first 24 hours and may comprise: pallor, nausea, vomiting, anorexia and abdominal pain, or patients may be asymptomatic. Liver damage, e.g. increased levels of hepatic transaminase (AST, ALT), lactate dehydrogenase and bilirubin, together with increased prothrombin levels may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. Paracetamol overdose may cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, which may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. On initial presentation, the patient's symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported. Overdose may also result in disseminated intravascular coagulation.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for

immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N- acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the

antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics: codeine and paracetamol.
ATC code: N02AJ06.

Paracetamol is a well-established analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract.

Codeine is a centrally acting weak analgesic. Codeine exerts its effects through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract. Concentration in plasma reaches a peak in 10-60 minutes after ingestion depending on the pharmaceutical formulation.

Codeine phosphate is well absorbed after oral administration and is widely distributed.

Distribution
Paracetamol is relatively uniformly distributed throughout most body fluids. Plasma protein binding is variable.

Codeine is widely distributed throughout most body fluids and exhibits low plasma protein binding with a plasma half-life of approximately 2.5 to 3 hours.

Biotransformation

Paracetamol is mainly metabolized in the liver, following two major metabolic pathways, with formation of glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalyzed by the Cytochrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinone imine) which under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Codeine is metabolized in the liver by the hepatic enzyme Cytochrome P450 2D6 (CYP2D6) to form morphine, and Cytochrome (CYP3A4) to form norcodeine, which are further metabolized by conjugation with glucuronic acid.

Elimination

Less than 5% is excreted as unmodified paracetamol; the elimination half-life varies from 1 to 4 hours. Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60- 80%) and sulfate conjugates (20-30%). In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects.

About 86% of *codeine* is excreted in the urine in 24 hours, 40-70% is free or conjugated codeine, 5-15% is free or conjugated morphine and 10-20% is free or conjugated norcodeine.

5. PHARMACOLOGICAL PROPERTIES

5.3 Preclinical Safety Data

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

starch, pre-gelatinised
povidone
maize starch
talc
magnesium stearate
stearic acid
microcrystalline cellulose
croscarmellose sodium
lactose monohydrate
hypromellose
macrogol

quinoline yellow (E104)
erthyrosine (E127)
titanium dioxide (E171)

6.2 Incompatibilities

None.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store this medicine in a safe and secure storage space, where other people cannot access it. It can cause serious harm and be fatal to people when it has not been intended for them.

6.5 Nature and contents of container

PVC 250 µm / aluminium foil 20 µm or 30 µm blisters in outer cartons, containing 6, 10, 12, 16, 20, 24, 30 or 32 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Omega Pharma Ltd,
Wrafton, Braunton,
Devon, EX33 2DL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 02855/0074

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2024

10 DATE OF REVISION OF THE TEXT

23/03/2026