SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paramol Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 500mg
Dihydrocodeine Tartrate 7.46mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone and as an antipyretic in conditions such as: headache; migraine period pain; toothache and other dental pain; back pain; muscular and joint pains and neuralgia.

4.2 Posology and method of administration

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms.

Posology

Adults:

One or two tablets every four to six hours.
Do not exceed 8 tablets in any 24 hour period.

Do not take for more than 3 days continuously without medical review.

Paediatric Population

Adolescents 16 years old and over:
One or two tablets every four to six hours.
Do not exceed 8 tablets in any 24 hour period.

Do not take for more than 3 days continuously without medical review.

Adolescents 12–15 years old:
One tablet every four to six hours.
Do not exceed 4 tablets in any 24 hour period.

Do not take for more than 3 days continuously without medical review.

Children under 12 years:
The product 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 section 4.4).

Special Populations

Hepatic Impairment: Patients with hepatic impairment should seek the advice of a doctor before taking this product (see section 4.4). Dosage should be reduced in chronic hepatic disease.

Renal Impairment: Patients with renal impairment should seek the advice of a doctor before taking this product (see section 4.4).

Elderly Population: Caution should be exercised with use of the product in the elderly (see section 4.4). A healthcare professional should be consulted to determine if a dosage reduction is necessary.

Method of Administration

For oral administration. Paramol Tablets should, if possible be taken during or after meals.

4.3 Contraindications

Hypersensitivity to paracetamol, dihydrocodeine tartrate or to any of the excipients listed in section 6.1

Diarrhoea caused by poisoning until the toxic material has been eliminated, or diarrhoea associated with pseudomembranous colitis.

Acute alcoholism, convulsive disorders, head injuries, and conditions in which intracranial pressure is raised.

Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions.

In pregnancy and breast-feeding (see section 4.6).

Obstructive airways disease

Respiratory depression.

Delayed gastric emptying and paralytic ileus.

In all paediatric patients (0 to 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.

4.4 Special warnings and precautions for use

Paramol Tablets should be given with caution to patients with allergic disorders and should not be given during an attack of asthma.
Dosage should be reduced in hypothyroidism and in chronic hepatic disease. An overdose can cause hepatic necrosis.

Paracetamol
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. Do not take with any other paracetamol-containing products. Immediate medical advice should be sought in the event of an overdose, even if you feel well (see section 4.9).
Do not take concurrently with any other codeine-containing compounds.

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 malnutrition and 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.

Dihydrocodeine
Care is advised in the administration of dihydrocodeine to patients with hypotension, asthma (avoid during an acute attack), decreased respiratory reserve, acute respiratory depression, obstructive airways disease, head injuries and conditions in which intracranial pressure is raised, adrenocortical insufficiency, prostatic hypertrophy, hypothyroidism, shock, obstructive and inflammatory bowel disorders, acute abdominal conditions (e.g. peptic ulcer) or a history of a peptic ulcer, recent gastrointestinal surgery, gallstones and diseases of the biliary tract, myasthenia gravis, a history of arrhythmias, convulsions and in also patients with a history of drug abuse, acute alcoholism, or emotional instability. This product should be avoided in patients with risk of paralytic ileus.

Dosage should be reduced in the elderly. Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults. Dihydrocodeine should be used with caution in the elderly and debilitated patients as they may be more susceptible to the respiratory depressant effects (see section 4.2).

Prolonged regular use of dihydrocodeine, 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.

If you are being prescribed medicines, seek the advice of a doctor before taking this product.

Care is advised in the administration of this product in patients with severe renal or severe hepatic impairment (hepatic disease).

Dihydrocodeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic effects. 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 low doses.

CYP2D6 metabolism: 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 metabolisers in different populations are summarized below:

Population	Prevalence %
African/ Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2.0%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1.0 to 2.0%

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

Concomitant use of Paramol 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 Paramol 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).

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: Dihydrocodeine 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.

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 opioid dosage using best practices for opioid taper.

Hyperalgesia: Hyperalgesia has been reported with the use of opioids, particularly following long-term use and/or at high doses. Hyperalgesia may resolve with opioid dose reduction, discontinuation, or switching to a different opioid.

Hepatobiliary disorders: Dihydrocodeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms including gallstones and pancreatitis. Therefore, dihydrocodeine/ibuprofen has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

4.5 Interaction with other medicinal products and other forms of interaction

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

Antiemetics: The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.

Cholestyramine: Paracetamol absorption may be reduced by cholestyramine.

Isoniazid: The toxicity of paracetamol may be increased by isoniazid.

Liver enzyme-inducing drugs: Drugs which induce or regulate liver microsomal enzymes such as anticonvulsants (including phenytoin, barbiturates, carbamazepine) and alcohol, may increase the hepatotoxic potential of paracetamol.

Hydroxyzine: Concurrent use of hydroxyzine (anxiolytics) with dihydrocodeine may result in increased analgesia as well as increased central nervous system depressant, sedative and hypotensive effects.

Central Nervous System Depressants: The depressant effects of opioids are enhanced by depressants of the central nervous system such as other opiods, alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants, antipsychotics and phenothiazines.

Diuretics and Antihypertensives: The hypotensive actions of diuretics and antihypertensive agents may be potentiated when used concurrently with opioid analgesics.

Antidiarrhoeal and Anti-peristaltic agents: Concurrent use of codeine/dihydrocodeine with antidiarrhoeal and antiperistaltic agents such as loperamide and kaolin may increase the risk of severe constipations.

Antimuscarinics: Concomitant use of antimuscarinics or medications with muscarinic action (e.g. atropine and some antidepressants) may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

Neuromuscular Blocking Agents: The respiratory depressant effect caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

Anticholinergic agents: Concomitant use of opiate agonists and drugs with anticholinergic activity may increase the risk of urinary retention or severe constipation, which can lead to paralytic ileus.

Quinidine: Quinidine can inhibit the analgesic effect of dihydrocodeine.

Abiraterone: Abiraterone might reduce analgesic effect of dihydrocodeine by CYP2D6 inhibition.

Mexiletine: Opioids (including Dihydrocodeine) may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

Metoclopramide, cisapride and domperidone: Dihydrocodeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.

Cimetidine: Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.
Naloxone: Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.

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).

Interference with laboratory tests:
Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

Serotonergic drugs: Serotonin syndrome has been reported during concomitant use of serotonergic drugs including triptans, selective serotonin-reuptake inhibitors (SSRI's), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), and tricyclic antidepressants, with opioids at recommended dosages.

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).

4.6 Fertility, Pregnancy and lactation

Pregnancy

There is potential for respiratory depression in the neonate.

The product is contraindicated throughout pregnancy (see section 4.3).

Breastfeeding

The product is contraindicated in breast-feeding (see section 4.3).

Fertility

Unknown

4.7 Effects on ability to drive and use machines

Opioid analgesics can impair mental function and can cause blurred vision, dizziness, drowsiness, double vision, confusion, hallucinations, orthostatic hypotension and convulsions (see section 4.8).

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

Paracetamol
Adverse effects of paracetamol are rare.

Dihydrocodeine
Regular prolonged use of dihydrocodeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is stopped. Prolonged use of a painkiller for headaches can make them worse.
Adverse events which have been associated with paracetamol at OTC doses (maximum 4000 mg per day) and dihydrocodeine tartrate, in short term use, are given below, tabulated by system organ class and frequency. Frequencies are defined as: Very common (≥1/10); Common (≥1/100 and <1/10); Uncommon (≥1/1000 and <1/100); Rare (≥1/10,000 and <1/1000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System Organ Class	**Frequency**	**Adverse Events**
Blood and Lymphatic System Disorders	Not known	Thrombocytopenia[a], agranulocytosis[a1]
Immune System Disorders	Not known	Urticaria[b], pruritus[b], face oedema[b].
Metabolism and Nutrition Disorders	Not known	High anion gap metabolic acidosis[2] Decreased appetite[b]
Psychiatric Disorders	Not known	Depression[b], hallucination[b], confusional state[b], dependence[b], mood altered[b], restlessness[b], nightmare[b]
Nervous System Disorders	Not known	Dizziness[b], drowsiness[b], convulsion[b], intracranial pressure increased[b], headache[b] , dyskinesia[b]
Eye Disorders	Not known	Vision blurred[b], diplopia[b], miosis[b]
Ear and Labyrinth Disorders	Not known	Vertigo[b]
Cardiac Disorders	Not known	Bradycardia[b], palpitations[b], tachycardia[b]
Vascular Disorders	Not known	Orthostatic hypotension[b]
Respiratory, Thoracic and Mediastinal	Not known	Respiratory depression[b], dyspnoea[b], cough

System Organ Class	Frequency	Adverse Events
Disorders		suppression[b]
Gastrointestinal Disorders	Not known	Abdominal pain[b], nausea[b], constipation[b], vomiting[b], dry mouth[b], incontinence[b], diarrhoea[b], large intestinal obstruction[b], faecaloma[b], pancreatitis[b]
Hepatobiliary Disorders	Not known	Biliary colic[b], sphincter of Oddi dysfunction[b]
Skin and Subcutaneous Tissue Disorders	Not known	Rash[ab], flushing[b]
	Very rare	Cases of serious skin reactions have been reported. Skin reactions (Stevens-Johnson Syndrome[a], toxic epidermal necrolysis[a], acute generalised exanthematous pustulosis[a3])
Musculoskeletal and Connective Tissue Disorders	Not known	Muscle rigidity[b]
Renal and Urinary Disorders	Not known	Ureteric colic[b], micturition disorder[b4]
Reproductive System and Breast Disorders	Not known	Libido decrease[b]
General Disorders and Administration Site Conditions	Not known	Hypothermia[b], hyperhidrosis[b], irritability[b], fatigue[b], malaise[b]

Description of Selected Adverse Reactions

[1] There have been occasional reports of blood dyscrasias, including thrombocytopenia, agranulocytosis and haemolytic anaemia, but these were not necessarily causally related

[2] 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.[3] Serious hypersensitivity reactions have been reported (see section 4.4).
[4] Dysuria, increased frequency, decrease in amount.
Active Ingredients:
[a] Paracetamol; [b] Dihydrocodeine tartrate

Reporting of Suspected Adverse Reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

Immediate medical advice should be sought in the event of an overdose, even if you feel well. Liver damage is possible 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:

An increased risk of liver damage from paracetamol overdosing has been associated with:

a, Patients on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b, Patients who consumes ethanol in excess of recommended amounts.

Or

c, Patients likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Or

d, Patients taking isoniazid

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. 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. Overdose may result in disseminated intravascular coagulation.

Management

Immediate treatment is essential in the management of a 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.

Dihydrocodeine

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

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 pin-point 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Analgesics, Anilides; ATC Code: N02BE51

Paracetamol is an effective analgesic possessing a remarkably low level of side effects. It's broad clinical utility has been extensively reported and now largely replaces aspirin for routine use. Paracetamol is well tolerated, having a bland effect on the gastric mucosa, unlike aspirin, it neither exacerbates symptoms of peptic ulcer nor precipitates bleeding. Dihydrocodeine Tartrate has been widely used for a number of years as a powerful analgesic. 30mg of dihydrocodeine has the analgesic potency of 60 to 120mg of codeine. In addition the product exhibits well defined anti-tussive activity. Fortifying paracetamol with dihydrocodeine tartrate provides an effective combination of drugs for the treatment of mild to moderate pain and acts as an anti-pyretic.

5.2 Pharmacokinetic properties

Dihydrocodeine is well absorbed from the gastrointestinal tract. Like other Phenanthrene derivatives, dihydrocodeine is largely metabolised in the liver with the resultant metabolites being excreted mainly in the urine. Metabolism of dihydrocodeine includes O-demethylation, N-Demethylation and 6-Ketoreduction. Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring 30 minutes to 2 hours after ingestion. It is metabolised in the liver, and excreted in the urine mainly as glucuronide and sulphate conjugates.

5.3 Preclinical safety data

There are no preclinical tests performed on the product.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium Stearate
Maize Starch
Povidone
Opadry Y-1-7000

6.2 Incompatibilities

None stated

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

250µ PVC base material with an aluminium foil 20µ coated with a 15µ PVC layer containing 12, 24, or 32 tablets.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

RECKITT BENCKISER HEALTHCARE (UK) LIMITED
103-105 BATH ROAD
SLOUGH
BERKSHIRE
SL1 3UH
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00063/0693

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/09/1999 / 02/03/2009

10 DATE OF REVISION OF THE TEXT

30/12/2025