Summary of Product Characteristics

1. Name of the medicinal product

CODAMOL RUSAN
Paracetamol & Codeine Phosphate Tablets

2. Qualitative and quantitative composition

Kindly refer section 6.1

3. Pharmaceutical form

TABLETS

4. Clinical particulars

4.1 Therapeutic indications

CODAMOL- RUSAN is indicated in children 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

CODAMOL- RUSAN 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. Maximum daily dose should not exceed 8 tablets in any 24 hour period.

Adults and children aged 16 years to 18 years: 1-2 tablets which may be repeated every 6 hours.

Paediatric population:

Children aged 12 years to 15 years:

The recommended CODAMOL- RUSAN dose for children 12-15 years should be 1 tablet which may be repeated every 6 hours when necessary up to a maximum dose of 4 tablets in any 24 hour period.

Children aged less than 12 years:

CODAMOL- RUSAN 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: Dosage should be reduced in the elderly where there is impairment of hepatic function.

For oral administration.

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.

4.3 Contraindications

• Hypersensitivity to the active substances, other opioids 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 pseudomembraneous colitis
• respiratory depression
• obstructive airways 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 lifethreatening adverse reactions
• in women during breastfeeding
• in patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

4.4 Special warnings and precautions for use
CODAMOL- RUSAN should be used with caution in patients with:
• hepatic function impairment (avoid if severe) and those with non-cirrhotic alcoholic liver disease. The hazards of overdose are greater in those with alcoholic liver disease..
• Prolonged use of CODAMOL- RUSAN may cause hepatic necrosis.
• renal function impairment
• hypothyroidism (risk of depression and prolonged CNS depression is increased)
• inflammatory bowel disease - risk of toxic megacolon
• Opioids should not be administered during an asthma attack
• convulsions - may be induced or exacerbated
• drug abuse, dependence (including alcoholism), enhanced instability, suicidal ideation or attempts - predisposed to drug abuse
• head injuries or conditions where intracranial pressure is raised
• gall bladder disease or gall stones - opioids may cause biliary contraction
• gastro-intestinal surgery - use with caution after recent GI surgery as opioids may alter GI motility
• prostatic hypertrophy or recent urinary tract surgery
• adrenocortical insufficiency, eg Addison's Disease
• hypotension and shock
• myasthenia gravis
• phaeochromocytoma - opioids may stimulate catecholamine release by inducing the release of endogenous histamine
Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.
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 extensive or 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, 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:

Summary of Product Characteristics

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

Paediatric population

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 .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.

Label Warnings:

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, because of the risk of delayed, serious liver damage.

or if leaflet present:

Immediate medical advice should be sought in the event of an overdose, even if you feel well.

The label will state:

Front of Pack

• Can cause addiction.

• For three days use only.

Back of Pack

• For the short term treatment of acute moderate pain when other painkillers have not worked. Do not take less than four hours after taking other painkillers.

• If you need to take this medicine for more than three days you must see your doctor or pharmacist.

• This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

The leaflet will state:

Headlines section

• This medicine can only be used for the short term treatment of acute moderate pain when other painkillers have not worked. Do not take less than four hours after taking other painkillers.

• You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice.

• This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.

• If you take this medicine for headaches for more than three days it can make them worse.

Summary of Product Characteristics

Section 1: What the medicine is for
• For the short term treatment of acute moderate pain when other painkillers have not worked. Do not take less than four hours after taking other painkillers.
Section 2: Before taking
• This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
• If you take a painkiller for headaches for more than three days it can make them worse.

4.5 Interaction with other medicinal products and other forms of interaction
Paracetamol can interact with the following:
• Drugs which alter gastric emptying time (eg cimetidine, ethyl alcohol, oral steroid contraceptives). These drugs reduce or delay peak paracetamol blood levels.
• Metoclopramide or domperidone increases the speed of absorption of paracetamol.
• Colestyramine reduces paracetamol absorption.
• Drugs which interfere with the metabolism of paracetamol by competition with metabolic pathways or substrates eg anticonvulsants (phenytoin), hepatic enzyme inducers, alcohol, barbiturates, tricyclic antidepressants. A poor diet (low protein) may also have a similar effect on the risk of serious paracetamol toxicity to hepatic enzyme inducers. Patients who have taken barbiturates, tricyclic antidepressants and alcohol may show diminished ability to metabolise large doses of paracetamol, the plasma half-life of which may be prolonged.
• The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
• Alcohol can increase the hepatotoxicity of paracetamol overdosage and may have contributed to the acute pancreatitis reported in one patient who had taken an overdosage of paracetamol.
Codeine Phosphate can interact with the following:
• CNS depressants - enhanced sedative and/or hypotensive effect with alcohol, anaesthetics, hypnotics, anxiolytics, antipsychotics, hydroxyzine, tricyclic antidepressants
• Antibacterials, eg ciprofloxacin, - avoid premedication with opioids as reduced plasma ciprofloxacin concentration
• MAOIs - use only with extreme caution
• Cyclizine
• Mexiletine - delayed absorption
• Metoclopramide and domperidone - antagonise GI effects
• Cisapride - possible antagonism of GI effects
• Dopaminergics (eg selegiline) - possible risk of hyperpyrexia and CNS toxicity. This risk is greater with pethidine but with other opioids the risk is uncertain
• Ulcer healing drugs - cimetidine inhibits the metabolism of opioid analgesics.
• Anticholinergics (eg atropine) - risk of severe constipation which may lead to paralytic illness, and /or urinary retention
• Antidiarrhoeal drugs (eg loperamide, kaolin) - increased risk of severe constipation
• Antihypertensive drugs (eg guanethidine, diuretics) - enhanced hypotensive effect
• Opioid antagonists (eg buprenorphine, naltrexone, naloxone)
• Neuromuscular blocking agents - additive respiratory depressant effects.

Summary of Product Characteristics

4.6 Fertility, pregnancy and lactation

Pregnancy

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

Breast-feeding

Codeine should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

Opioid analgesics can impair mental function and can cause blurred vision and dizziness. Patients should make sure they are not affected before driving or operating machinery.

4.8 Undesirable effects

At the recommended dosage, paracetamol may cause the following side effects:

• Allergic reactions - rare but may include skin rash, drug fever, mucosal lesions.

• Effects on CNS - drowsiness, impaired mental functions• Effects on GI system - Chronic hepatic necrosis • Effects on CVS - toxic myocarditis.

• Effects on blood - blood dyscrasias • Effects on GU system - Nephrotoxicity • Other effects - Most reports of adverse reactions to paracetamol relate to overdosage with the drug. Very rare cases of skin reactions have been reported.

Adverse effects of opioid treatment which have been reported include:

• Allergic reactions (may be caused by histamine release) • Effects on CNS - confusion, drowsiness, vertigo, dizziness, changes in mood, hallucinations, CNS excitation (restlessness/excitement), convulsions, mental depression, headache, trouble sleeping, or nightmares, raised intracranial pressure, tolerance or dependence.• Effects on GI system - constipation, GI irritation, biliary spasm, nausea, vomiting, loss of appetite, dry mouth, paralytic ileius or toxic megacolon.• Effects on CVS - bradycardia, palpitations, hypotension.

• Effects on sensory system • Effects on GU system - ureteral spasm, antidiuretic effect.

• Other effects - trembling, unusual tiredness or weakness, malaise, miosis, hypothermia.

• Effects of withdrawal - abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, nausea, vomiting, sweating and increase in heart rate, respiratory rate and blood pressure. NOTE - tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

4.9 Overdose

Paracetamol:

Symptoms: Pallor, nausea, vomiting, anorexia and abdominal pain in the first 24 hours. 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, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias have been reported.

Liver damage is likely in adults who have taken 10g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Treatment: Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any patient who had ingested around 7.5g or more of paracetamol in the

preceding 4 hours should undergo gastric lavage. Administration of oral methionine or intravenous N-acetylcysteine which may have a beneficial effect up to at least 48 hours after the overdose, may be required. General supportive measures must be available.
Opioids:
Symptoms: cold clammy skin, confusion, convulsions, severe drowsiness, tiredness, low blood pressure, pinpoint pupils of eyes, slow heart beat and respiratory rate coma.
Treatment: Treat respiratory depression or other life-threatening adverse effects first. Empty the stomach via gastric lavage or induction of emesis.
The opioid antagonist naloxone (0.4-2mg subcutaneous) can be given and repeated at 2-3 minute intervals to a maximum of 10mg. Naloxone may also be given by intramuscular injection or intravenous infusion. The patient should be monitored as the duration of opioid analgesic may exceed that of the antagonist.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Paracetamol combinations excl. psycholeptics
ATC Code: N02B E51
Paracetamol has analgesic and antipyretic properties but is has no useful anti-inflammatory properties.
Codeine phosphate is a weak analgesic and is used in the treatment of cough and diarrhoea.
Paracetamol's effects are thought to be related to inhibition of prostaglandin synthesis.
Codeine is much less potent than morphine and it is inadequate against severe pain even in the largest tolerable doses. It does not cause appreciable respiratory depression but does have antitussive and constipating effects. Codeine is a centrally acting weak analgesic. Codeine exerts its effect 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.
Codeine produces its analgesic effects by binding to μ opioid receptors. Codeine also binds weakly to κ opioid receptors which mediates spinal analgesia, sedation and miosis.

5.2 Pharmacokinetic properties

Codeine
Absorption and Distribution
Codeine and its salts are readily absorbed from the GI tract and ingestion of codeine phosphate produces peak plasma concentrations in about one hour.
Biotransformation and Excretion
It is metabolised in the liver; and codeine and its metabolites are entirely excreted almost by the kidney, mainly as conjugates with glucuronic acid. The plasma half-life is reported to be 3-4 hours after administration by mouth.
Paracetamol
Absorption and Distribution
Paracetamol is readily absorbed from the GI tract with peak plasma concentrations occurring about 30 minutes-2 hours after ingestion.
Biotransformation and Excretion
It is metabolised in the liver and excreted in the urine, mainly as the glucuronide and sulfate conjugates. The elimination half-life varies from about 1-4 hours.

Summary of Product Characteristics

Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.
A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

5.3 Preclinical safety data
Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients
Also contains: Pregelatinised Starch, Maize Starch, Povidone K30, Magnesium Stearate

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in a dry place at the temperature not exceeding 30^0C.
Keep out of reach of children.
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6.5 Nature and contents of container
10 tablets packed in an ALU-PVC blister.
Such 10 blisters to a carton.

6.6 Special precautions for disposal and other handling
Not applicable

7. Marketing authorisation holder

RUSAN PHARMA LTD

58-D, Government Industrial Estate, Charkop,
Kandivali (west), Mumbai 400067, India.

8. Marketing authorisation number(s)

XXXX

9. Date of first authorisation/renewal of the authorisation

XXXX

10. Date of revision of the text