Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Renlaucol 500 mg / 30 mg, effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500mg and Codeine Phosphate hemihydrate 30mg.
Excipients with known effect: Each tablet also contains 487 mg of sorbitol and 413 mg of sodium.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet

Bevelled, flat, round, white tablet with a scoreline on one face.
Although the tablets have a score line, they are not to be halved as they do not divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

RENLAUCOL 500 mg / 30 mg, effervescent tablets is indicated in the relief of severe pain in adults. Codeine is indicated in children older than 12 years of age for the treatment of acute moderate to severe 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 one or two tablets every four hours as required. The total daily dose should not exceed 4 g paracetamol (8 tablets in a day).

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

Paediatric population:

Children 12-18 years old (body weight >35 kg)
The dose should primarily be calculated based on the codeine component and body weight. 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. Maximum daily dose should not exceed 240 mg.

Children below the age of 12 years old
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 use.
The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

Duration of 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, 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.

Severe liver disease and severe renal impairment. The hazards of overdose could be greater in those with alcoholic liver disease.

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

In women during breastfeeding (see section 4.6).

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

4.4 Special warnings and precautions for use

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

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

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.

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.

<u>CYP2D6 metabolism</u>
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:

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%

Patients must be advised not to exceed the recommended dose.

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 this product, and to consult their doctor if symptoms persist.

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 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.

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

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains 17.9 mmol (413 mg) sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Concomitant administration of this product 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 following combinations with RENLAUCOL should be avoided: quinidine.
The following combinations with RENLAUCOL may require dose adjustment: neuroleptics, antidepressants, warfarin, enzyme-inducing medications such as certain antiepileptics (phenytoin, phenobarbital, carbamazepine), rifampicin and St John's wort (*Hypericum perforatum*), probenecid, metoclopramide, cholestyramine and chloramphenicol.

Codeine
Codeine is probably active through the codeine being O-demethylated to morphine via the enzyme CYP2D6. This bioactivation is inhibited by certain medications, e.g. quinidine, terbinafine, certain antidepressants and neuroleptics, etc. These drugs therefore counter the effect of codeine. This interaction has been documented in studies on healthy trial subjects and/or pilot studies on patients.
Direct studies have been performed with quinidine, which is a very strong inhibitor of CYP2D6, and this combination should therefore be avoided.
Neuroleptics and antidepressants also have an inhibiting effect on CYP2D6, which means that these combinations may require a dose adjustment.
Enzyme-inducing medications such as rifampicin, barbiturates, several antiepileptics, St John's wort (Hypericum perforatum), etc. can produce reduced plasma concentrations of morphine (see also interaction with paracetamol).

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. The effect may occur already at daily doses of 2000 mg after three days. Occasional doses of paracetamol do not have a significant effect on bleeding tendency. Increased monitoring of INR values should be done during the duration of the combination and after its discontinuation.

The metabolism of paracetamol is increased in patients taking substances known to induce liver enzymes (e.g. the antiepileptics carbamazepine, phenytoin, phenobarbital, primidone, as well as rifampicin and St John wort (Hypericum perforatum). This can increase the hepatotoxicity of paracetamol due to increased and more rapid formation of toxic metabolites. Isolated reports describe unexpected hepatotoxicity in patients taking phenobarbital, phenytoin, or carbamazepine after taking paracetamol. Therefore, caution should be taken in case of concomitant use of enzyme inducing substances.

Probenecid nearly halves the clearance of paracetamol by inhibiting its conjugation with glucuronic acid. This probably means that the dose of paracetamol can be halved when being given at the same time as probenecid.

The absorption of paracetamol may be enhanced by metoclopramide or domperidone, and absorption may be reduced by colestyramine. Cholestyramine should not be given within one hour if maximum analgesic effect is to be obtained.

Paracetamol may affect the pharmacokinetics of chloramphenicol. Therefore an analysis of chloramphenicol in plasma is recommended in the event of combination treatment with chloramphenicol for injection.

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.

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

This product is then not recommended during pregnancy.

Lactation:
Codeine must not be used during breastfeeding (see section 4.3). 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 metaboliser 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 is no information available concerning the effect of this medicinal product on fertility.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if this product causes dizziness or sedation. Codeine may cause 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.

System Organ Class	Very common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1000)	Not known (frequency cannot be estimated from the available data)
Blood and lymphatic system disorders		blood dyscrasias (including thrombocytopenia and agranulocytosis)*	
Immune system disorders		hypersensitivity including skin rash*	
Nervous system disorders	Dizziness, Light-headedness, Sedation, Headache		Confusion
Eye disorders			Miosis
Psychiatric disorders	Dysphoria, Euphoria		
Respiratory, thoracic and mediastinal disorders	Shortness of breath		
Gastrointestinal disorders	Nausea, Vomiting, Constipation, Abdominal pain		
Skin and subcutaneous tissue disorders	Pruritus, Rash, Urticaria		
Renal and urinary disorders			Urinary retention

*Adverse reactions observed with the use of paracetamol-containing products

Codeine can cause respiratory depression particularly in overdosage and in patients with compromised respiratory function (see Section 4.9).

Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.

Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Codeine
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.

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
Because of its ready availability, paracetamol is often taken in overdosage. Toxicity is likely if more than 150 mg/kg of paracetamol is ingested. The major complication is acute hepatic necrosis, although without treatment fewer than 10% of unselected patients are at risk of severe liver damage (plasma aminotransferase > 1000 mg/l). About 1% develop fulminant hepatic failure which is usually fatal. Renal failure from acute tubular necrosis is a further uncommon complication which may develop in the absence of hepatic failure. There are no specific early manifestations of severe paracetamol poisoning. Consciousness is not impaired except in the occasional unusually severely poisoned patient with metabolic acidosis, and maximum abnormality of liver function tests is delayed for at least 3 days.

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

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: Other analgesics and antipyretics, Anilides.
Paracetamol, combinations excl. psycholeptics
ATC Code: N02BE51

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).

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

The conversion of codeine to morphine is effected by the CYP2D6. Well-characterised genetic polymorphism in CYP2D6 lead to the inability to covert codeine to morphine, thus making codeine ineffective as an analgesic for about 7% of the Caucasian population (see also section 4.4).

The fixed combination of paracetamol and codeine showed to be effective in nociceptive pain. However, data in chronic pain, cancer pain and neuropathic pain are lacking.

5.2 Pharmacokinetic properties

Absorption and distribution
Paracetamol is rapidly and completely absorbed after oral administration, with peak plasma concentrations occurring between 15 min and 2 h after ingestion. 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. Paracetamol is extensively metabolised in the liver and the total body clearance is about 5 ml/min/1/kg. Some 2-5% of a therapeutic dose of paracetamol is excreted unchanged in the urine.

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

Due to genetic polymorphism in the liver enzyme CYP2D6 some patients have a deficiency to convert codeine to morphine leading to an inadequate analgesic effect. On the other hand there are patients who are extensive or ultra-rapid metabolisers. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. For further information see also section 4.4.

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 SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydrogen carbonate
Sodium carbonate anhydrous
Citric acid anhydrous
Sodium Docusate
Sorbitol
Saccharin Sodium
Dimeticone
Sodium Benzoate
Macrogol 6000
Natural grapefruit flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months for polypropylene tubes. Use within 2 years of first use.
12 months for foil strips

6.4 Special precautions for storage

For the foil strips:
This medicinal product does not require any special storage conditions.

For the polypropylene tubes:
Store in the original tubes. Keep the tubes tightly closed.

6.5 Nature and contents of container

Aluminium/polyethylene foils strips of 4, 8, 16, 32 and 100 effervescent tablets.

Polypropylene tubes of 8, 16, 32 and 96 effervescent tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

MG Pharma
24 rue Erlanger,
75016 Paris,
France

8 MARKETING AUTHORISATION NUMBER

PA1811/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd May 2014

10 DATE OF REVISION OF THE TEXT

September 2014