Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lemsip Multirelief capsules Paracetamol 500mg Phenylephrine hydrochloride 6.1mg Guaifenesin 100mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains paracetamol 500mg, phenylephrine hydrochloride 6.1mg and guaifenesin 100mg
For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard
Capsules with a red cap and green body, printed 'Lemsip' on the cap in white ink, containing white, free flowing powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of symptoms of cold and influenza, including the relief of aches and pains, sore throat, headache, nasal congestion, lowering of temperature and chesty coughs.

4.2 Posology and method of administration

Patients should consult a doctor or pharmacist if symptoms persist for more than 3 days, or worsen.

Posology:
Adults, elderly and children (aged16 years and over): Two capsules every 4-6 hours as required.
Do not take more than 8 capsules (4 doses) in 24 hours.
Do not give to children under 16 years of age.

Hepatic impairment:
Paracetamol should be used with caution in patients with hepatic impairment as a reduced dose or prolonged dosing interval may be necessary (see section 4.4).

Renal impairment:
Paracetamol should be used with caution in patients with renal impairment as a reduced dose and/or prolonged dosing interval may be necessary (see section 4.4).

Adults:

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

Elderly Population: Experience has indicated that normal adult dosage of paracetamol is usually appropriate. However, in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

The maximum daily dose of paracetamol should not exceed 60 mg/kg/day (up to a maximum of 2 g per day) in the following situations, unless directed by a physician:

- Weight less than 50 kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Method of Administration
For oral administration. Swallow whole with water. Do not chew.

4.3 Contraindications

- Hypersensitivity to any of the active substances or any of the excipients listed in section 6.1.
- Severe coronary heart disease and cardiovascular disorders.
- Hypertension.
- Hyperthyroidism.
- Contraindicated in patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors (MAOI).
- Concomitant use of other sympathomimetic decongestants.

4.4 Special warnings and precautions for use

Use with caution in patients with Raynaud's Phenomenon or diabetes mellitus. Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Patients should be advised not to take other paracetamol -containing products concurrently.

Immediate medical advice should be sought in the event of an overdose, even if the patient feels well because of the risk of delayed serious liver damage (see section4.9). Use with caution in patients with porphyria.

Phenylephrine should be used with care in patients with closed angle glaucoma and prostatic enlargement.

The product should not be used during pregnancy unless recommended by a healthcare professional (see section 4.6).

Use during breastfeeding should be avoided, unless recommended by a healthcare professional (see section 4.6).

To be used with caution in patients with phaeochromocytoma.

This medicine contains less than 1 mmol sodium (23mg) per capsule, essentially "sodium free".

Not recommended for concomitant use with a cough suppressant.

Do not exceed the stated dose.

Serious skin reactions, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP), have been reported very rarely in association with paracetamol. These severe hypersensitivity reactions are potentially life threatening. The product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. See section 4.8.

Respiratory: This product should not be used for persistent or chronic cough such as that occurring with smoking, asthma, chronic bronchitis or emphysema, or for cough associated with excessive phlegm. A persistent cough may be indicative of a serious condition. If cough persists, a physician should be consulted.

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.

Hepatotoxicity at therapeutic dose: Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or mor risk factors for hepatotoxicity including low body weight (<50kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors. Caution is also advised in patients on

concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2 and 4.9).
Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatotoxicity which may warrant dosage adjustment.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol
The rate of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption may be reduced by cholestyramine.

Medicinal products which induce hepatic microsomal enzymes, such as alcohol, barbiturates, monoamine oxidase inhibitors and tricyclic antidepressants, may increase the hepatotoxicity of paracetamol, particularly after overdose.

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.

Phenylephrine hydrochloride:
Monoamine oxidase inhibitors (including moclobemide): hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors (see section 4.3).

Sympathomimetic amines: concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.

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

Cholestyramine: Paracetamol absorption may be reduced by cholestyramine.

Oxytocic agents: The vasopressor effect of sympathomimetics such as phenylephrine may be potentiated when used in conjunction with oxytocic drugs such as oxytocin and ergot alkaloids which can increase risk of haemorrhagic stroke.

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

Liver enzyme-inducing drugs: Drugs which induce or regulate liver microsomal enzymes (cytochrome p-450 isoenzyme 2E1), such as anticonvulsants (including phenytoin, barbiturates, carbamazepine) and alcohol, may increase the hepatotoxic potential of paracetamol.

Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa): phenylephrine may reduce the efficacy of beta-blockers and antihypertensives. The risk of hypertension and other cardiovascular side effects may be increased (see section 4.3).

Tricyclic antidepressants (e.g. amitriptyline): may increase the risk of cardiovascular side effects with phenylephrine (see section 4.3).

Digoxin and cardiac glycosides: concomitant use of phenylephrine may increase the risk of irregular heartbeat or heart attack.

Guaifenesin:
Guaifenesin may interfere with diagnostic measurements of urinary 5-hydroxy-indoleactic acid or vanillylmandelic acid. If urine is collected within 24 hours of a dose of the medicinal product, a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).
Guaifenesin: May increase the rate of absorption of paracetamol.

Flucloxacillin:
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
The product should not be used during pregnancy unless recommended by healthcare professional.

The safety of this medicine during pregnancy and lactation has not been established but in view of a possible association of foetal abnormalities with first trimester exposure to phenylephrine, the use of the product during pregnancy should be avoided. In addition, because phenylephrine may reduce placental perfusion, the product should not be used in patients with a history of pre-eclampsia.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage.

There are limited data on the use of guaifenesin in pregnant women. Guaifenesin has been linked with an increased risk of neural tube defects in a small number of women with febrile illness in the first trimester of pregnancy.

Breast-feeding
The product should be avoided during lactation unless recommended by a healthcare professional. There are limited data on the use of phenylephrine in lactation. Paracetamol is excreted in breast milk, but not in a clinically significant amount. Available published data do not contraindicate breast feeding. There is no information on the use of guaifenesin in lactation.

Fertility
There are no available data regarding the effects of the active ingredients on fertility.

4.7 Effects on ability to drive and use machines

Lemsip Multi-Relief Capsules has no or negligible influence on ability to drive or use machinery.

4.8 Undesirable effects

Adverse events which have been associated with paracetamol, guaifenesin and phenylephrine 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	Haemopoietic disorders[1]
Immune System Disorders	Not known	Hypersensitivity
Metabolism and Nutrition Disorders	Not known	High anion gap metabolic acidosis[2]
Nervous System Disorders	Not Known	Headache
Cardiac Disorders	Not Known	Palpitations
Vascular Disorders	Not Known	Hypertension
Gastrointestinal Disorders	Not known	Abdominal discomfort, nausea, vomiting, diarrhoea
Skin and Subcutaneous Tissue Disorders	Very rare Not known	Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis[3], Skin rash
Renal and Urinary Disorders	Not known	Urinary retention[4]

Description of Selected Adverse Reactions
[1] There have been reports of blood dyscrasias including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis, but these were not necessarily causally related to paracetamol.
[2] 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] Very rare cases of serious skin reactions have been reported.
[4] Especially in males

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Immediate medical advice should be sought in the event of an overdose, even if you feel well. The main cause for concern in overdosage with this product is paracetamol intake.

Paracetamol:

Paracetamol overdose can result in liver damage which may be fatal. Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk Factors

If the patient:

1. Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes. **or**
2. Regularly consumes ethanol in excess of recommended amounts. **or**
3. Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia. **or**
4. Is taking isoniazid

Symptoms
Symptoms of paracetamol overdose 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. CNS stimulation and delirium may occur initially, followed by CNS depression, stupor, hypothermia, rapid shallow breathing, hypotension and circulatory failure. Shock may also develop, as well as seizures and coma. Cardiac arrhythmias and pancreatitis have been reported.

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 24 hours from ingestion should be discussed with the NPIS or a liver unit.

Phenylephrine hydrochloride:

Features of severe overdose of phenylephrine include haemodynamic changes and cardiovascular collapse with respiratory depression. Treatment includes symptomatic and supportive measures. Hypertensive effects may be treated with an i.v. alpha-receptor-blocking agent.

Phenylephrine overdose is likely to result in: nervousness, headache, dizziness, insomnia, increased blood pressure, nausea, vomiting, mydriasis, acute angle closure glaucoma (most likely to occur in those with closed angle glaucoma), weakness, tremor, tachycardia, palpitations, allergic reactions (e.g. rash, urticaria, allergic dermatitis), dysuria, urinary retention (most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy).

Additional symptoms may include hypertension, and possibly reflex bradycardia. In severe cases confusion, seizures, arrhythmias and hallucinations may occur. However the amount required to produce serious phenylephrine toxicity would be greater than that required to cause paracetamol-related liver toxicity.

Treatment should be as clinically appropriate. Severe hypertension may need to be treated with alpha blocking medicinal products such as phentolamine.

Guaifenesin: Very large doses may cause nausea and vomiting. The drug is, however, rapidly metabolised and excreted in the urine. Patients should be kept under observation and treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N02B E51

Paracetamol: Paracetamol has both analgesic and antipyretic activity, which is believed to be mediated principally through its inhibition of prostaglandin synthesis within the central nervous system.

Phenylephrine hydrochloride: Phenylephrine is a post-synaptic alpha-receptor agonist with low cardioselective beta-receptor affinity and minimal central stimulant activity. It is a recognised decongestant and acts by vasoconstriction to reduce oedema and nasal swelling.

Guaifenesin: Guaifenesin is an expectorant which increases the volume and reduces the viscosity of tenacious sputum.

5.2 Pharmacokinetic properties

Paracetamol: Paracetamol is absorbed rapidly and completely from the small intestine, producing peak plasma levels after 15-20 minutes following oral dosing. The systemic availability is subject to first-pass metabolism and varies with dose between 70% and 90%. The drug is rapidly and widely distributed throughout the body and is eliminated from plasma with a T½ of approximately 2 hours. The major metabolites are glucuronide and sulphate conjugates (>80%) which are excreted in urine.

Phenylephrine hydrochloride: Phenylephrine is absorbed from the gastrointestinal tract, but has reduced bioavailability by the oral route due to first-pass metabolism. It retains activity as a nasal decongestant when given orally, the drug distributing through the systemic circulation to the vascular bed of the nasal mucosa. When taken by mouth as a nasal decongestant phenylephrine is usually given at intervals of 4-6 hours.

Guaifenesin: Guaifenesin is absorbed from the gastrointestinal tract. It is metabolised and excreted in the urine.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Maize starch
Croscarmellose sodium
Sodium laurilsulfate

Magnesium stearate
Talc

Capsule shell:
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)
Brilliant blue - FD&C blue 1 (E133)

Printing ink:
Shellac (E904)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

250 micron opaque uPVC blister with foil/paper laminate, 35 gsm paper/micron soft-temper foil and heat-seal coated, contained in an outer cardboard carton.

Pack sizes: 2, 4, 6, 8, 10, 12, 14 and 16.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Ireland Ltd
7 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT