SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

LemoCalm Max Strength Cold and Flu Relief Powder For Oral Solution
Well Pharmaceuticals Cold and Flu relief Powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 1000 mg Paracetamol and 10 mg Phenylephrine hydrochloride.

Excipients with known effect: Also contains 2355 mg of sucrose,75 mg of aspartame and 139.03 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution
Creamy, yellow-white granule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Adults, the elderly and children aged 16 years and above:
One sachet dissolved by stirring in hot water, but not boiling water and sweetened to taste. Not more than four sachets to be taken in 24 hours. The dose may be repeated in 4-6 hours.

Children under 16 years:
Not recommended for children under 16 years of age.

Method of administration
Oral administration after dissolution in water.

4.3. Contraindications

- Hypersensitivity to paracetamol, phenylephrine hydrochloride or to any of the excipients listed in section 6.1
- Concomitant use of other sympathomimetic decongestants
- Severe coronary heart disease and cardiovascular disorders
- Hypertension
- Diabetes mellitus
- Contraindicated in patients with phaeochromocytoma
- Avoid in patients with prostatic enlargement
- Hyperthyroidism
- Closed angle glaucoma
- Contraindicated in patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors (see section 4.5).
- Beta-blockers

4.4 Special warnings and precautions for use

Paracetamol

Prolonged or frequent use is discouraged. Patients should be advised not to take other Paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In adolescents treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised in the administration of Paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatic insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (child-pugh>9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, hemolytic anemia, alcohol abuse dehydration and chronic malnutrition (see section 4.2).

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.

The hazards of overdose are greater in those with non- cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2 grams in such case. Alcohol should not be used during the treatment with Paracetamol.

Caution is advised in asthmatic patients sensitive to aspirin, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5% of the patients tested.

Phenylephrine

Phenylephrine should be used with care in patients with cardiovascular disease, diabetes mellitus, closed angle glaucoma, prostatic enlargement and hypertension.

Phenylephrine hydrochloride may increase blood pressure and therefore special care is advisable in individuals receiving antihypertensive treatment. Caution should also be exercised by individuals taking beta-adrenergic blocking agents.

Use with caution in occlusive vascular disease (Raynaud's syndrome) or diabetes mellitus.

Important information regarding the ingredients of this medicine

Aspartame: This medicinal product contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

Sucrose: This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose- galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine**.**

Sodium: The maximum daily dose of this product is equivalent to 27.81 % of the WHO recommended maximum daily intake for sodium. This medicinal product is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The risk of hepatotoxicity of paracetamol may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, and alcohol.

Probenecid causes an almost 2-fold reduction in clearance of Paracetamol by inhibiting its conjugation with glucuronid acid. A reduction of the Paracetamol dose should be considered for concomitant treatment with probenecid.

- Salicylamide may prolong the elimination t1/2 of Paracetamol
- Metoclopramide and Domperidone: accelerate absorption of Paracetamol
- Cholestyramine: reduces absorption of Paracetamol
- Concomitant use of Paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation. 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.
- Isoniazid: Reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver.
- Lamotrigine: Decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of its metabolism in the liver.

Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxydase-peroxydase.

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).

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.

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.

4.6. Fertility, pregnancy and lactation

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 if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Following oral administration, Paracetamol is excreted into breast milk in small quantities. To date, no adverse reactions or undesirable effects are known in association with lactation. Therapeutic doses of Paracetamol can be administered during breast-feeding.

There is no evidence from non-clinical studies indicating effects of paracetamol on male or female fertility at clinically relevant doses.

Phenylephrine hydrochloride

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.

In view of the lack of data on the use of phenylephrine during lactation, this medicine should not be used during breast feeding.

The effects of phenylephrine on male or female fertility have not been studied.

4.7 Effects on ability to drive and use machines

This product has no or negligible influence on ability to drive or use machinery.

4.8 Undesirable effects

Paracetamol

The frequency using the following convention: very common (> 1/10); common (>1/100 to < 1/10); uncommon (>1/1000 to < 1/100); rare (>1/10000 to < 1/1000); very rare (< 1/10000), including isolated reports; not known: frequency cannot be estimated from the available data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Symptoms
Blood and lymphatic system disorders	Rare	Platelet disorders, stem cell disorders.
	Very Rare	thrombocytopenia leukopenia neutropenia hemolytic anaemia agranulocytosis[1]
	Not Known	pancytopenia
Immune system disorders	Rare	Allergies (excluding angioedema).
Metabolism and nutrition disorders	Very Rare	Hypoglycaemia
	Not known	High anion gap metabolic acidosis
Psychiatric disorders	Rare	Depression NOS, confusion, hallucinations.
Nervous system disorders	Very Rare	Tremor NOS, headache NOS
Eye disorders	Rare	Abnormal vision.
Cardiac disorders	Rare	Oedema.
Gastrointestinal disorders	Rare	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
Hepato-biliary disorders	Rare	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
	Very Rare	Hepatotoxicity
Skin and subcutaneous tissue disorders	Rare	Pruritus, rash, sweating, purpura, angioedema, urticaria. Very rare cases of serious skin reactions have been reported.
Renal and urinary disorders	Very Rare	Sterile pyuria (cloudy urine) and renal side effects
	Not Known	Urinary retention[2]
General disorders and administration site conditions	Rare	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
	Very Rare	hypersensitivity reaction (requiring discontinuation of treatment)
Injury, poisoning and procedural complications	Very Rare	Overdose and poisoning

Not known: Some cases of edema of the larynx, anaphylactic shock, anaemia, bronchospasm*, liver alteration and hepatitis, renal alteration (severe renal impairment,

nephrite interstitial, haematuria, anuresis), gastrointestinal effects and vertigo have been reported.

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

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] Especially in males

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.

Phenylephrine

The following adverse events have been observed in clinical trials with phenylephrine and may therefore represent the most commonly occurring adverse events.

Body System	**Undesirable effect**
Psychiatric disorders	Nervousness, irritability, restlessness, and excitability
Nervous system disorders	Headache, dizziness, insomnia
Cardiac disorders	Increased blood pressure
Gastrointestinal disorders	Nausea, Vomiting.

Adverse reactions identified during post-marketing use are listed below. The frequency of these reactions is unknown but likely to be rare.

Eye disorders	Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma
Cardiac disorders	Tachycardia, palpitations
Skin and subcutaneous disorders	Allergic reactions (e.g. rash, urticaria, allergic dermatitis). Hypersensitivity reactions – including that cross-sensitivity may occur with other sympathomimetics
Renal and urinary disorders	Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

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

If the patient

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

Or

b. Regularly consumes ethanol in excess of recommended amounts.

Or

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

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.

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.

Phenylephrine hydrochloride

Symptoms

Features of severe overdose of phenylephrine include haemodynamic changes and cardiovascular collapse with respiratory depression, seizures and arrhythmias. However, smaller amounts of the paracetamol and phenylephrine hydrochloride combination product would be required to cause paracetamol related liver toxicity than to cause serious phenylephrine-related toxicity. Treatment includes early gastric lavage and 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, reflex bradycardia, mydriasis, acute angle closure glaucoma (most likely to occur in those with closed angle glaucoma), 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, hallucinations, seizures and arrhythmias may occur. However the amount required to produce serious phenylephrine toxicity would be greater than that required to cause paracetamol-related liver toxicity.

Management

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Anilides
ATC Code: N02BE51. Paracetamol, combinations excl. psycholeptics

Paracetamol

In therapeutic doses, paracetamol has antipyretic and mild analgesic actions. These effects are thought to be related to inhibition of prostaglandin synthesis within the central nervous system.

Phenylephrine hydrochloride

Phenylephrine is sympathomimetic post-synaptic α_1-adrenergic receptor agonist with low cardioselective beta receptor affinity and minimal central nervous stimulant activity. It is a recognised decongestant and acts by vasoconstriction to reduce oedema and nasal swelling. It has a weak α_2-adrenoceptor agonist activity and some activity as a β-adrenoceptor. It is also termed a sympathomimetic vasoconstrictor. Its efficacy as a decongestant results from its vasoconstrictor properties. Vasoconstriction within the nasal mucosa decreases the volume of mucosal tissue and decreases the resistance to air flow through the nasal passages.

5.2 Pharmacokinetic properties

Paracetamol

Absorption

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low.

Metabolism

Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulphuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cystein and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination

Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.
Elimination half life is about 2 hours.

Physiopathological Variations
Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly Subjects. The capacity for conjugation is not modified.

Phenylephrine
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 nasal mucosa. When taken by mouth as a nasal decongestant phenylephrine is usually given at intervals of 4 – 6 hours.

5.3 Preclinical safety data

Paracetamol
In animal studies investigating the acute, sub chronic and chronic toxicity of paracetamol in the rat and mouse, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma and necrosis were observed. These changes are, on the one hand, attributed to the mechanism of action and, on the other, to the metabolism of paracetamol. The metabolites that is probably responsible for the toxic effects and the corresponding organic changes have also been found in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. At sub toxic doses, symptoms of intoxication can occur following a 3-week intake period. Paracetamol should therefore not be administered over a long period of time or at high doses.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Extensive investigations showed no evidence of any relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice yielded no evidence on relevant carcinogenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol crosses the placental barrier. Animal studies and clinical experience to date have not indicated any teratogenic potential.

Phenylephrine
There is no evidence to indicate mutagenic potential of phenylephrine. There is no reported carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate
Citric acid
Tartaric acid
Pregelatinised maize starch
Lemon juice
Ascorbic acid
Aspartame (E951)
Natural colour
Lemon flavour

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

The product is packed in laminate sachets comprising paper (45 gsm gloss coated paper) / polythene (12 gsm) / aluminium foil (8 micron) / polythene (25 gsm). Five or ten sachets may be contained in a box board carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 17907/0164

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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