

## **LEMSIP MAX COLD AND FLU RELIEF CAPSULES**

**PL 00063/0164**

**UKPAR**

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## **LEMSIP MAX COLD AND FLU RELIEF CAPSULES**

**PL 00063/0164**

### **LAY SUMMARY**

The MHRA granted Reckitt Benckiser Healthcare (UK) Limited Marketing Authorisation (licence) for the medicinal product Lemsip Max Cold & Flu Relief Capsules (PL 00063/0164). This is a general sale list (GSL) product.

Lemsip Max Cold and Flu Relief Capsules consists of a combination of ingredients which are effective in relieving different symptoms of colds and flu.

Paracetamol is a well known pain killer (Analgesic). It is effective against aches and pains, including headache. It can also reduce fever (Antipyretic).

Phenylephrine hydrochloride reduces swelling in the passages of the nose (nasal decongestant) and so relieves a blocked nose.

Lemsip Max Cold& Flu Relief Capsules also contain caffeine, which acts as a mild stimulant.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Lemsip Max Cold & Flu Relief Capsules outweigh the risks, hence marketing authorisation has been granted.

## **LEMSIP MAX COLD AND FLU RELIEF CAPSULES**

**PL 00063/0164**

### **SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisation for the medicinal product Lemsip Max Cold & Flu Relief Capsules (PL 00063/0164) to Reckitt Benckiser Healthcare (UK) Limited on 3<sup>rd</sup> March 2008. This is a General Sale List (GSL) product used for the relief of symptoms associated with the common cold and influenza, including relief of aches and pains, sore throat, headache, fatigue and drowsiness, nasal congestion and lowering of temperature.

This is a simple abridged application submitted under article 10.c. This product claims to be a generic medicinal product of Lemsip Max Cold and Flu Capsules PL 00063/0104 held by Reckitt Benckiser Healthcare (UK) Limited, granted in 1998.

**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.

**Caffeine:** Caffeine is a central nervous system stimulant. It inhibits the enzyme phosphodiesterase and has an antagonistic effect at central adenosine receptors. Its action on the central nervous system is mainly on the higher centres and it produces a condition of wakefulness and increased mental activity.

**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.

## **PHARMACEUTICAL ASSESSMENT**

**LICENCE NO:** PL 00063/0164

**PROPRIETARY NAME:** Lemsip Max Cold & Flu Relief Capsules

**COMPANY NAME:** Reckitt Benckiser Healthcare (UK) limited

**E.C. ARTICLE:** Article 10 (c) of Directive 2001/83/EC

**LEGAL STATUS:** GSL

### **1 INTRODUCTION**

This national simple abridged application is for Lemsip Max Cold and Flu Relief Capsules. The product is indicated for the relief of symptoms associated with the common cold and influenza, including relief of aches and pains, sore throat, headache, fatigue and drowsiness, nasal congestion and lowering of temperature.

This application was submitted under Article 10(c) of Directive 2001/83/EC, claiming to possess the same qualitative and quantitative composition in terms of the active substance and the same pharmaceutical form of an already authorised product. The relevant product in the UK is Lemsip Max Cold and Flu Capsules (PL00063/0104) authorised to Reckitt Benckiser Healthcare (UK) limited, granted in 1998.

### **2 MARKETING AUTHORISATION APPLICATION (MAA)**

#### **2.1 Name(s)**

The proposed name of the product is Lemsip Max Cold & Flu Relief Capsules. The product has been named in line with current requirements.

#### **2.2 Strength, pharmaceutical form, route of administration, container and pack sizes**

The product contains the active ingredients paracetamol, caffeine and phenylephrine hydrochloride. It will be packaged into opaque UPVC/aluminium paper blisters only. The packaging is identical to the blister packaging used for the reference product.

The respective SPC have indicated that Lemsip Max Cold & Flu Relief Capsules are packed in pack sizes of 4, 6, 8, 12, and 16 capsules. The same pack sizes are stated in the reference product. The proposed shelf life is 3 years which is identical to the reference product. The proposed storage condition is also consistent with the details registered for the cross-reference product.

#### **2.3 Legal status**

The product is General Sale List (GSL).

#### **2.4 Marketing authorisation holder/Contact Persons/Company**

The proposed Marketing Authorisation holder is Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, East Yorkshire, HU8 7DS, United Kingdom. The QP responsible for pharmacovigilance is stated and a CV is included.

## **2.5 Manufacturers**

The proposed manufacturing sites are consistent with that registered for the cross-reference product and evidence of GMP compliance has been provided. A flow diagram showing the sequence and activities of the different sites involved in the manufacturing process has been provided.

## **2.6 Qualitative and quantitative composition**

The proposed compositions are consistent with the details registered for the cross-reference product.

## **2.7 Manufacturing process**

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

## **2.8 Finished product/shelf-life specification**

The proposed finished product specification is in line with the details registered for the cross-reference product.

## **2.9 Drug substance specification**

The proposed drug substance specification conformed to current Ph Eur monograph for the actives and was consistent with that of the reference product.

Current Ph Eur certificate of suitability for the drug substance manufacturer has been provided to support the sources of active substances. This manufacturer is in line with the reference product.

## **2.10 TSE Compliance**

The active ingredient supplier has confirmed that no materials of human or animal origin have been used in the manufacture of the actives.

Appropriate TSE declarations have been provided for magnesium stearate used in the finished product.

## **2.11 Bioequivalence / Bioavailability**

No bioavailability and bioequivalence data are required to support this informed consent application as the proposed product is manufactured to the same formula utilising the same process. The finished product manufacturing site is also identical to that used by the reference product.

## **3 EXPERT REPORT**

The applicant has included detailed expert reports of the application. Signed declarations and copies of the experts' CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

## **4. PRODUCT NAME & APPEARANCE**

See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

## **5. SUMMARY OF PRODUCT CHARACTERISTICS**

The proposed SmPCs are consistent with the details registered for the cross-reference product.

## **6. PATIENT INFORMATION LEAFLET/BLISTER**

PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

The proposed artwork complies with the relevant statutory requirements.

## **7. CONCLUSIONS**

The data submitted with the application is acceptable. Marketing Authorisation should be granted.

## **PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none is required for an application of this type.



## **CLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none is required for an application of this type.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for application of this type.

### **EFFICACY**

This application is identical to previously granted application for Lemsip Max cold & Flu Capsules.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with the actives is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

**LEMSIP MAX COLD AND FLU RELIEF CAPSULES****PL 00063/0164****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation application on 26 <sup>th</sup> May 2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 12 <sup>th</sup> July 2005
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 28 <sup>th</sup> July 2005, 8 <sup>th</sup> November 2005, and 3 <sup>rd</sup> August 2007
4	The applicant responded to the MHRA's request, providing further information for the quality section on 15 <sup>th</sup> September 2005, 7 <sup>th</sup> April 2006, and 16 <sup>th</sup> September 2007
5	The application was determined on 3 <sup>rd</sup> March 2008

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Lemsip Max Cold & Flu Relief Capsules.

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient	mg/Capsule
Paracetamol	500
Caffeine	25
Phenylephrine hydrochloride	6.1

For excipients, see 6.1.

### 3. PHARMACEUTICAL FORM

Capsules, hard.

Red cap and yellow body with 'Lemsip' printed on the cap.

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic indications

For the relief of symptoms associated with the common cold and influenza, including relief of aches and pains, sore throat, headache, fatigue and drowsiness, nasal congestion and lowering of temperature.

#### 4.2. Posology and method of administration

Adults (over 12 years): Two capsules every 4 hours to a maximum of four doses in any 24 hours.

Do not exceed eight capsules in any 24 hours.

Children 6-12 years: One capsule every 4 hours to a maximum of four doses in any 24 hours.

Do not exceed four capsules in any 24 hours.

Swallow whole with water. Do not chew.

Not recommended for children under 6 years of age.

#### 4.3. Contraindications

Paracetamol: Hypersensitivity to paracetamol or any of the other constituents.

Caffeine: Should be given with care to patients with a history of peptic ulcer.

Phenylephrine hydrochloride: Severe coronary heart disease and cardio-vascular disorders. Hypertension. Hyperthyroidism. Contraindicated in patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors.

#### 4.4. Special warnings and precautions for use

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.

Use with caution in patients with Raynaud's Phenomenon and diabetes mellitus.

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

Leaflet: 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.

Do not exceed the stated dose. Do not take with any other paracetamol-containing products. If symptoms persist consult your doctor. Keep out of the reach of children. If you are pregnant or are being prescribed medicine by your doctor, seek his advice before taking this product. Contains paracetamol (panel).

#### **4.5. Interactions with other medicinal products and other forms of interaction**

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

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.

Phenylephrine may adversely interact with other sympathomimetics, vasodilators and beta-blockers. Drugs which induce hepatic microsomal enzymes, such as alcohol, barbiturates, monoamine oxidase inhibitors and tricyclic antidepressants, may increase the hepatotoxicity of paracetamol, particularly after overdosage. Contraindicated in patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors because of a risk of hypertensive crisis.

#### **4.6. Pregnancy and lactation**

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.

Paracetamol is excreted in breast milk, but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

Caffeine: Taken during pregnancy it appears that the half-life of caffeine is prolonged. This is a possible contributing factor in hyperemesis gravidarum.

Phenylephrine hydrochloride: Due to the vasoconstrictive properties of phenylephrine the product should be used with caution in patients with a history of pre-eclampsia. Phenylephrine may reduce placental perfusion and the product should be used in pregnancy only if the benefits outweigh this risk. There is no information on use in lactation.

#### **4.7. Effects on ability to drive and use machines**

None known.

#### **4.8. Undesirable effects**

Adverse effects of paracetamol are rare, but hypersensitivity including skin rash may occur. There have been a few reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Phenylephrine hydrochloride: High blood pressure with headache, vomiting and rarely, palpitations. Also rare reports of allergic reactions. If taken close to bedtime, may interfere with sleep.

#### **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 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. 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 or 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 NPIS or a liver unit.

Caffeine: Symptoms - emesis and convulsions may occur. No specific antidote. However, treatment is usually fluid therapy. Fatal poisoning is rare. If symptoms become apparent or overdose is suspected, consult a doctor immediately.

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

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.

Caffeine: Caffeine is a central nervous system stimulant. It inhibits the enzyme phosphodiesterase and has an antagonistic effect at central adenosine receptors. Its action on the central nervous system is mainly on the higher centres and it produces a condition of wakefulness and increased mental activity.

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.

ATC Classification: NO2B E51

**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 T<sub>1/2</sub> of approximately 2 hours. The major metabolites are glucuronide and sulphate conjugates (>80%) which are excreted in urine.

Caffeine: Caffeine is absorbed readily after oral, rectal or parenteral administration, but absorption from the gastrointestinal tract may be erratic. There is little evidence of accumulation in any particular tissue. Caffeine passes readily into the central nervous system and into saliva. Concentrations have also been detected in breast milk. It is metabolised almost completely and is excreted in the urine as 1-methyluric acid, 1-methylxanthine and other metabolites with only about 1% unchanged.

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.

**5.3. Preclinical safety data**

No preclinical findings of relevance have been reported.

**6. PHARMACEUTICAL PARTICULARS****6.1. List of excipients**

Capsule Contents

Maize Starch,

Croscarmellose,

Sodium laurilsulfate

Magnesium stearate,

Talc (E553b),

Capsule Body and Cap

Gelatin

Quinoline yellow (E104),

Titanium dioxide (E171),

Erythrosine (E127),

Patent blue V (E131),

Shellac (E904),

Tartrazine (E102)

Aluminium hydroxide.

**6.2. Incompatibilities**

Not applicable.

**6.3. Shelf life**

Three years.

**6.4. Special precautions for storage**

Do not store above 25°C.

**6.5. Nature and contents of container**

250 micron opaque uPVC/20 micron aluminium foil blister, heat-seal coated, contained in an outer cardboard box.

Pack sizes: 4, 6, 8, 12 and 16 capsules.

**6.6 Instruction for use and handling**

The capsules are to be taken orally, with water if preferred, and swallowed whole without being chewed.

**7. MARKETING AUTHORISATION HOLDER**

Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS, East Yorkshire, United Kingdom.

**8. MARKETING AUTHORISATION NUMBER**

PL 00063/0164.

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

03/03/2008

**10. DATE OF REVISION OF THE TEXT**

03/03/2008



## PATIENT INFORMATION LEAFLET

### **Lemsip Max Cold & Flu Relief Capsules**

#### **Patient Information Leaflet**

**Please read this leaflet carefully before you take this medicine.  
If you are not sure about anything, ask your pharmacist or doctor.**

#### **What are Lemsip Max Cold & Flu Relief Capsules?**

Each capsule contains the active ingredients paracetamol 500 mg, phenylephrine hydrochloride 6.1 mg and caffeine 25 mg. The other ingredients are starch, croscarmellose, sodium laurilsulfate, magnesium stearate, talc (E5536), gelatin, titanium dioxide (E171), quinoline yellow (E104), patent blue V (E131), erythrosin (E127), shellac (E904), tartrazine (E102) and aluminium hydroxide.

Lemsip Max Cold & Flu Relief Capsules are available in cartons 4, 6, 8, 12 or 16.

#### **What are Lemsip Max Cold & Flu Relief Capsules used for?**

Lemsip Max Cold & Flu Relief Capsules consist of a combination of ingredients which are effective in relieving different symptoms of colds and flu.

Both of these common illnesses are caused by virus infections. Cold symptoms include a runny or blocked nose, sneezing, and possibly a headache or sore throat. Flu symptoms include more severe headache, aches and pains, fever and tiredness, usually needing a day or two in bed.

Paracetamol is a well known pain killer (analgesic). It is effective against aches and pains, including headache. It can also reduce fever (antipyretic).

Phenylephrine hydrochloride reduces swelling in the passages of the nose (nasal decongestant) and so relieves a blocked nose.

Lemsip Max Cold & Flu Relief Capsules also contain caffeine, which acts as a mild stimulant.

It is important to drink plenty of liquid when suffering from colds or flu.

#### **Before taking Lemsip Max Cold & Flu Relief Capsules**

**Do not take with any other paracetamol-containing products.** Do not take with large quantities of alcohol.

As with all medicines, Lemsip Max Cold & Flu Relief Capsules may not be suitable for some people.

#### **Do not take this medicine if:**

- you have problems with an overactive thyroid, or
- you have a serious heart condition, or
- you have high blood pressure (hypertension), or
- you are allergic to any ingredient, or
- you are taking or have taken monoamine oxidase inhibitors (MAOI antidepressants) within 14 days.

**You should ask the pharmacist** before taking Lemsip Max Cold & Flu Relief Capsules if:

- you are pregnant, have Raynaud's syndrome (blood circulation problem), diabetes, or
- you have problems with your liver, kidneys, or a history of peptic ulcer, or
- you are taking beta-blockers for high blood pressure, or vasodilators or
- you are taking tricyclic antidepressants, other decongestants or barbiturates, or
- you are taking other medicines. Some drugs may affect the absorption of paracetamol, including those used to treat blood cholesterol (cholestyramine) and nausea and vomiting (metoclopramide and domperidone). The effect of blood thinning drugs (warfarin and other coumarins) may be increased by paracetamol.

This product also contains tartrazine (E102) which may cause allergic reactions.

### **How to take Lemsip Max Cold & Flu Relief Capsules**

The capsules should be swallowed whole with water. Do not chew.

### **How much to take**

**The dosage for adults and children over 12** is two capsules every 4 hours.

**Do not take more than eight capsules in 24 hours.**

**Children 6 - 12 years:** one capsule every 4 hours. **Not more than 4 capsules in any 24 hours. Not recommended for children under 6 years of age.**

**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.**

If the symptoms of your cold or flu persist for more than three days, or worsen, consult your pharmacist.

### **What side-effects may occur?**

Side-effects are rare. Reactions such as skin rashes, blood reactions (like a reduction in blood platelets or in white blood cells) or high blood pressure with headache, vomiting and rarely, palpitations, may occasionally occur. Caffeine, if taken close to bedtime, may interfere with sleep. Tell your doctor or pharmacist if you have any side-effects after taking this product.

### **Storage**

Keep all medicines safely away from children.


Do not use after the expiry date (EXP month/year) shown on the pack.

Do not store above 25°C (77°F).

### **Makers of Lemsip Max Cold & Flu Relief Capsules**

Marketing Authorisation Holder/Manufacturer: Reckitt Benckiser Healthcare (UK) Limited, Hull, HU8 7DS.

PL00063/0164

Lemsip, Lemsip Max and  are trade marks.

Leaflet last revised Jan 2006.

LABELLING



