SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Restocin tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains

- Paracetamol BP 500 mg
- Phenylephrine Hydrochloride BP 5 mg
- Chlorpheamine Maleate BP 2 mg
- Anhydrous Caffeine BP 30 mg

Excipients with known effect

- Each tablet contains 30 mg lactose
- Colour.: Ponceau 4R (Supra)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
A clear colourless to yellowish Solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of symptoms associated with the pain and congestion of sinusitis, including relief of aches and pains, headache, nasal congestion and lowering of temperature

4.2 Posology and method of administration

Lemsip Decongestant & Flu Capsules with caffeine is contraindicated in children under the age of 12 years (see section 4.3).
The patient should consult a doctor, if symptoms worsen or persist for up to 3 days. Paracetamol-containing products should be used at the lowest effective dose for the shortest possible time. The maximum daily dose must not be exceeded.

Posology
Adults, the elderly and adolescents aged 16 years and over: Two capsules every 4 hours to a maximum of four doses in any 24 hours.

Do not exceed eight capsules in any 24 hours.

In all patients over 16 years of age, 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: (see section 4.4)

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

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).

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).

The elderly
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 (see section 4.4).

Paediatric population under 16 years

- Children (12-15 years): 1 capsule every 4-6 hours when necessary to a maximum of 4 doses in 24 hours.
- Do not give to children under 12 years of age.
- Method of administration
- For oral administration. Swallow whole with water. Do not chew.

4.3 Contraindications

Use in children under 12 years of age.

Hypersensitivity to paracetamol, phenylephrine, caffeine or to any of excipients listed in section 6.1.

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

Phenylephrine hydrochloride: 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, or

who are currently receiving other sympathomimetic drugs, or have glaucoma or urinary retention.

4.4 Special warnings and precautions for use

Serious skin reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and acute generalised exanthematous

pustulosis, 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.

Care is advised in the administration of paracetamol to patients with hepatitis, non-cirrhotic alcoholic liver disease, hepatic insufficiency or renal insufficiency are at an increased risk of adverse reactions associated with paracetamol use. These patients should seek the advice of a doctor before taking this product. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

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

Due to the presence of caffeine, the product should be taken with care in patients with a history of peptic ulcers.

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

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, breast feeding or are being prescribed medicine by your doctor, seek his advice before taking this product. Contains paracetamol (panel). In children 12-15 years do not take with other cough and cold medicines.

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.

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration

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 more risk factors for hepatotoxicity including low body weight (<50 kg), 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.

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

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 medical assistance should be

sought immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOIs): Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors (see section 4.3).

Cardiac glycosides: Concomitant use of cardiac glycosides (e.g. digoxin) with phenylephrine may increase the risk of irregular heartbeat or heart attack.

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

Sympathomimetic agents: Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of hypertension and other cardiovascular side effects. Phenylephrine may reduce the efficacy of beta–blockers, vasodilators and other antihypertensives.

Anticoagulants: 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.

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

Cholestyramine: Paracetamol absorption may be reduced by cholestyramine.

CYP Inhibitors: Caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450. Factors known to alter the activity of this enzyme system may influence caffeine clearance. For example, caffeine elimination is inhibited by cimetidine, disulfiram, and oral contraceptive steroids. Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias.

Patient with prostatic hypertrophy may have increased difficulty with micturition. This product may act as a cerebral stimulant giving rise to insomnia, nervousness, hyperpyrexia, tremor and epileptiform convulsions.

Concurrent use of paracetamol and flucloxacillin is associated with an increased risk of metabolic acidosis, especially in patients with severe renal impairment, hepatic impairment, sepsis, malnutrition and chronic alcoholism.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

There is a possible association of foetal abnormalities with first trimester exposure to phenylephrine. 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.

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

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

Breast-feeding

The product should be avoided during lactation unless recommended by a healthcare professional.

There are limited data on the use of phenylephrine during lactation.

Whilst caffeine is excreted into breast milk at levels which are considered not to present a hazard to the infant, irritability and poor sleeping patterns have been reported.

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

Fertility

No known effects.

4.7 Effects on ability to drive and use machines

The product contains caffeine, a central nervous stimulant which helps counteract drowsiness and restore alertness. These effects are usually considered to have a positive influence on the ability to drive or operate machinery. However, dizziness and agitation have been reported with caffeine use (see section 4.8); affected patients should not drive or use machinery.

4.8 Undesirable effects

Adverse events which have been associated with paracetamol, phenylephrine and caffeine 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 Adverse Events	Frequency	Adverse Events
Blood and Lymphatic System Disorders	Not known	Thrombocytopenia, agranulocytosis 1
Psychiatric Disorders	Not known	Insomnia, restlessness, anxiety, agitation
Nervous System Disorders	Not known	Headache, dizziness
Cardiac Disorders	Rare	Palpitations

Vascular Disorders	Not known	Hypertension
Gastrointestinal Disorders	Not known	Gastric ulcer, epigastric discomfort, nausea, vomiting
Skin and Subcutaneous Tissue Disorders	Rare	Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulolsis Skin rash
		Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute
Renal and Urinary Disorders	Not known	Urinary retention

Description of Selected Adverse Reactions

1. There have been a few reports of blood dyscrasias, including thrombocytopenia and agranulocytosis, but these were not
2. necessarily causally related to paracetamol.
3. Serious hypersensitivity reactions have been reported (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 national reporting system listed in Appendix V.

4.9 Overdose

Paracetamol overdose can result in liver damage which may be fatal.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue. Some patients may be at increased risk of liver damage from paracetamol toxicity: Risk factors include;

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St.John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection,

starvation, cachexia

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Emergency Procedure:

Immediate transfer to hospital. Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines. Symptomatic treatment should be implemented.

Phenylephrine overdose is also likely to cause nausea and vomiting. In addition, other symptoms include nervousness, headache, dizziness, insomnia, hypertension, reflex bradycardia, mydriasis, acute angle closure glaucome (most likely to occur in those with closed angle glaucoma), tachycardia, palpitations, allergic reactions (e.g. rash, urticaria, allergic dermatitis) dysuria, and urinary retention (most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy). Features of severe overdose of phenylephrine include haemodynamic changes and cardiovascular collapse with respiratory depression, hallucinations, seizures and arrhythmias.

Symptoms of caffeine overdose are rare but emesis and convulsions may occur. Fatal poisoning is rare. If symptoms become apparent or overdose is suspected, consult a doctor immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Anilides; ATC Code: N02BE51

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. Phenylephrine is a sympathomimetic with mainly direct effects on adrenergic receptors.

It is a recognized decongestant and acts by vasoconstriction to reduce oedema and nasal swelling

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.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose
- Potassium Dihydrogen Phosphate
- Povidone (PVPK-30)
- Magnesium Stearate
- Purified Talc
- Sodium starch Glycolate (Type-A)
- Colour Ponceau 4R (Supra)
- Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Alu/Alu Blister

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: kalol,
District: Gandhinagar, Gujarat,
India.

8. MARKETING AUTHORISATION NUMBER(S)

TAN 20 H 0400

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25th September, 2020

10. DATE OF REVISION OF THE TEXT

Not Applicable (First authorization)