Sinarest® Tablets Lp NEW

1. Generic Name

Phenylephrine, Paracetamol, Levocetirizine

2. Qualitative and Quantitative composition

Phenylephrine	10mg
Paracetamol	500mg
Levocetirizine	2.5mg

3. Dosage form and strength

Oral tablets containing Phenylephrine 10mg, Paracetamol 500mg and Levocetirizine 2.5 mg.

4. Clinical particulars

4.1 Therapeutic indication

Sinarest LP new Tablet is indicated in treatment of common cold.

4.2 Posology and method of administration

The usual recommended oral dose of Sinarest LP new tablet for adult is one tablet twice a day.

4.3 Contraindication

The use of Sinarest LP new Tablet is contraindicated in patients with:

- Hypersensitivity to any ingredient in this product.
- End-stage renal impairment of less than 10 mL/min creatinine clearance or patients undergoing haemodialysis.
- Overactive thyroid, high blood pressure or heart disease.
- Severe hepatic dysfunction.
- On MAO inhibitors, hepatic impairment, severe renal failure, closed angle glaucoma.

4.4 Special warnings and precautions for use

- Caution in elderly patients, hyperthyroidism, myocardial disease, bradycardia, partial heart block or severe arteriosclerosis when administering phenylephrine.
- Caution in asthma, bladder neck obstruction, cardiovascular disease, COPD, GI obstruction, glaucoma, hepatic impairment, hyperthyroidism, increased intraocular pressure, malnutrition, renal impairment, elderly patients, and patients taking CNS depressants.
- Caution in severe hypovolemia if taking paracetamol products. Paracetamol: Risk for rare, but serious skin reactions that can be fatal; these reactions include StevensJohnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP); symptoms may include skin redness, blisters and rash.
- It is advisable not to drive or operate machinery when on treatment with Sinarest LP New Tablet.
- Use with caution in patients with Raynaud's phenomenon or diabetes. Patients with prostatic hypertrophy may have increased difficulty with micturition.
- Phenylephrine should be used with care in patients with closed angle glaucoma and prostatic enlargement.
- Avoid concurrent use of alcohol or other central nervous system depressants with Sinarest LP new tablet.
- To be sold by retail on the prescription of R.M.P only.
- Risk of medication errors and hepatotoxicity: Take care when prescribing and administering Sinarest LP New Tablet to avoid dosing errors which could result in accidental overdose and death.
- Sinarest LP New Tablet contains Paracetamol. Paracetamol has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of paracetamol at doses that exceed the maximum daily limits, and often involve more than one paracetamolcontaining product

4.5 Drug interactions

Phenylephrine: The co-administration of Monoamine Oxidase Inhibitors (MAOIs) or tricyclic antidepressants and an indirect or mixed-acting sympathomimetic may result in a hypertensive crisis and hence such concomitant use is best avoided. Additionally sympathomimetic may reduce the efficacy of beta-blocking and antihypertensive drugs.

Not recommended for patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors.

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

Paracetamol: Anticoagulant drugs (warfarin) - dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time Paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide.

Paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. antidepressants with anticholinergic properties, and narcotic analgesics Paracetamol may increase chloramphenicol concentrations.

The risk of paracetamol toxicity may be increased in patients receiving other hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents.

Paracetamol excretion may be affected when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour. Regular use of paracetamol possibly reduces metabolism of Zidovudine (increased risk of neutropenia).

Levocetirizine: In vitro data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drugmetabolizing enzymes. No in vivo drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with racemic cetirizine.

Antipyrine, Azithromycin, Cimetidine, Erythromycin, Ketoconazole, Theophylline, and Pseudoephedrine: Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole, and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect.

Ritonavir: Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.

4.6 Use in special population

- Pediatric: Do not exceed the recommended dose of 2.5 mg/day in children 6 to 12 years of age. The systemic exposure with the 5 mg dose is approximately twice that of adults.
- Geriatric: Elderly population may be at greater risk for the side-effects.
- Liver impairment: Use with caution.
- Renal failure: Use with caution.
- Pregnancy and lactation: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Sinarest LP new Tablet should be used during pregnancy only if clearly needed. As Levocetirizine is excreted in breast milk, Sinarest LP new Tablet is not recommended during breastfeeding.

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Sinarest LP new Tablet is known.

4.8 Undesirable effects

Sinarest LP new Tablet is generally well tolerated and adverse events are rare. Paracetamol is reported to show Fixed Drug Eruptions An adverse drug reaction includes urticaria, Stevens-Johnson syndrome, tachycardia, palpitations, headache, dizziness, nausea, fear, anxiety, restlessness, tremor, weakness, dysuria, insomnia, hallucinations & convulsions, anaemia, vertigo, dry mouth, cardiac arrest, tinnitus, thrombocytopenia, thyroid disorders, periorbital oedema, eye swelling, blurred vision, Eye pruritus, increased lacrimation, diarrhea, acute hepatic failure, hepatotoxicity, bronchospasm, respiratory arrest, hypotension, dyspepsia, sedation.

4.9 Overdose

There is limited experience of overdose with Sinarest LP new Tablets. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 Mechanism of action

Phenylephrine decreases nasal congestion by acting on α_1-adrenergic receptors in the arterioles of the nasal mucosa to produce constriction; this leads to decreased edema and increased drainage of the sinus cavities.

Paracetamol act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis. The antipyretic properties of acetaminophen are likely due to direct effects on the heat-regulating centres of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation.

Levocetirizine is an inverse agonist that decreases activity at histamine H1 receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms associated with seasonal and perennial allergic rhinitis. It does not prevent the actual release of histamine from mast cells.

The combination of Levocetirizine, Phenylephrine and Paracetamol in Sinarest LP New Tablet helps to relieve multiple symptoms of rhinosinusitis, colds and flu.

5.2 Pharmacodynamic properties

Paracetamol is a widely used analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. It is a major ingredient in numerous cold and flu medications and many prescription analgesics. It is extremely safe in standard doses, but because of its wide availability, deliberate or accidental overdoses are not uncommon. Paracetamol, unlike other common analgesics such as aspirin and ibuprofen, has no anti-inflammatory properties or effects on platelet function, and it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs or NSAIDs. At therapeutic doses Paracetamol does not irritate the lining of the stomach nor affect blood coagulation, kidney function, or the fetal ductus arteriosus (as NSAIDs can). Like NSAIDs and unlike opioid analgesics, Paracetamol does not cause euphoria or alter mood in any way. Paracetamol and NSAIDs have the benefit of being completely free of problems with addiction, dependence, tolerance and withdrawal. Paracetamol is used on its own or in combination with pseudoephedrine, dextromethorphan, Chlorpheniramine, diphenhydramine, doxylamine, codeine, hydrocodone, or oxycodone.

Phenylephrine is a powerful vasoconstrictor. It is used as a nasal decongestant and cardiotonic agent. Phenylephrine is a postsynaptic α1-receptor agonist with little effect on β-receptors of the heart. Parenteral administration of phenylephrine causes a rise in systolic and diastolic pressures, a slight decrease in cardiac output, and a considerable increase in peripheral resistance; most vascular beds are constricted, and renal, splanchnic, cutaneous, and limb blood flows are reduced while coronary blood flow is increased. Phenylephrine also causes pulmonary vessel constriction and subsequent increase in pulmonary arterial pressure.

Vasoconstriction in the mucosa of the respiratory tract leads to decreased edema and increased drainage of sinus cavities.

Studies in adult healthy subjects showed that levocetirizine at doses of 2.5 mg and 5 mg inhibited the skin wheal and flare caused by the intradermal injection of histamine.

5.3 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of Paracetamol varies from about 1 to 3 hours. Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged Paracetamol. A minor hydroxylated metabolite (Nacetyl-p-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after Paracetamol over dosage and cause tissue damage.

Phenylephrine has low oral bioavailability owing to irregular absorption and first-pass metabolism by monoamine oxidase in the gut and liver. When injected subcutaneously or intramuscularly it takes 10 to 15 minutes to act; subcutaneous and intramuscular injections are effective for up to about 1 hour and up to about 2 hours, respectively. Intravenous injections are effective for about 20 minutes. Systemic absorption follows topical application.

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet.
Levocetirizine is poorly metabolized and undergo renal excretion.

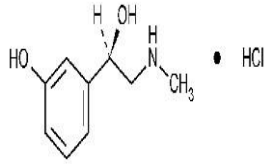
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

NA.

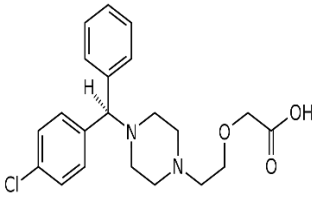
7. Description

Phenylephrine is in a class of medications called nasal decongestants. Its chemical name is hydrogen 3-[(1R)-1-hydroxy-2-(methylamino)ethyl] phenol chloride and its structural formula is:



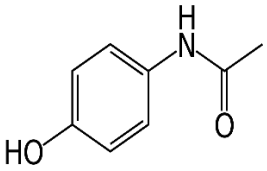
Its empirical formula is $C_9H_{13}NO_2$, and its molecular weight is 167.2 g/mol.

Levocetirizine is in a class of medications called antihistamines. Its chemical name is 2-(2-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetic acid dihydrochloride and its structural formula is:



Its empirical formula is $C_{21}H_{25}ClN_2O_3$, and its molecular weight is 388.8878 g/mol.

Paracetamol belongs to Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Its chemical name is N-acetyl-para-aminophenol (APAP) and its structural formula is:



Its empirical formula is $C_8H_9NO_2$ and its molecular weight is 155.19 g/mol.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Sinarest-LP New Tablets are available in blister strips of 10 tablets.

8.4 Storage and handling instructions

Store below 30 ºC in a dark and dry place.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by

Ravenbhel Healthcare Pvt. Ltd.

11. Details of permission or license number with date

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