Sinarest® New Tablets

1. Generic Name

Paracetamol, Phenylephrine, Chlorpheniramine maleate

2. Qualitative and Quantitative composition

Paracetamol	500mg
Phenylephrine	10mg
Chlorpheniramine maleate	2mg

3. Dosage form and strength

Uncoated tablets containing Paracetamol 500mg, Phenylephrine 10mg, Chlorpheniramine maleate 2mg for oral administration.

4. Clinical particulars

4.1 Therapeutic indication

Sinarest new Tablet is indicated for treatment of common cold.

4.2 Posology and method of administration

Adults: The usual recommended dose is one tablet thrice a day at 8 hourly intervals.

4.3 Contraindication

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

- Hypersensitivity to any of the ingredients of the formulation.
- Severe hypertension.
- 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 Stevens-Johnson 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 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.
- Chlorpheniramine, in common with other drugs having anticholinergic effects, should be used with caution in epilepsy; raised intra-ocular pressure including glaucoma; prostatic hypertrophy; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis or asthma; hepatic impairment; renal impairment.
- Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation (eg. increased energy, restlessness, nervousness). Should not be used with other antihistamine containing products, including antihistamine containing cough and cold medicines.
- 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 New Tablet to avoid dosing errors which could result in accidental overdose and death.

Sinarest 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 paracetamol-containing 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 anti-hypertensive 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).

Chlorpheniramine: Concurrent use of Chlorpheniramine and hypnotics or anxiolytics may cause an increase in sedative effects; therefore medical advice should be sought before taking Chlorpheniramine concurrently with these medicines. Chlorpheniramine inhibits phenytoin metabolism and can lead to phenytoin toxicity. The anti-cholinergic effects of Chlorpheniramine are intensified by MAOIs.

4.6 Use in special population

- Pediatric: Sinarest new tablet should be used with caution in children and generally avoided in those less than 2 years of age.
- Geriatric: Elderly population may be at greater risk for the side-effects.
- Liver impairment: Use with caution. Consult physician before use.
- Renal failure: Use with caution.
- Pregnancy and lactation: US Food and Drug Administration (FDA) has specified Chlorphenamine maleate as a pregnancy category B drug which indicates that animal and human studies have failed to demonstrate a risk to the fetus in any trimester. Paracetamol has been specified as a pregnancy category C drug which indicates that animal studies show an adverse effect on the fetus but there are no teratogenic studies of Paracetamol in pregnant women. Sinarest new Tablet is recommended to be taken during pregnancy only under doctor's recommendation**.**

4.7 Effects on ability to drive and use machine

It is advisable not to drive or operate machinery when on treatment with Sinarest new Tablet.

4.8 Undesirable effects

Sinarest new Tablet is generally well tolerated and adverse events are rare. 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, diarrhea, acute hepatic failure, hepatotoxicity, bronchospasm, respiratory arrest, hypotension, dyspepsia, sedation.

4.9 Overdose

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

5. Pharmacological properties

5.1 Mechanism of action

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.

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.

In allergic reactions an allergen interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to cell-degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H_1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. Chlorpheniramine maleate binds to the histamine H1 receptor. This block the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine.

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.

Chlorpheniramine maleate is a histamine H1 antagonist of the alkylamine class. It competes with histamine for the normal H1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and respiratory tract. It provides effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies.

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.

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract, peak plasma concentrations occurring about 2.5 to 6 hours after oral doses. Bioavailability is low, values of 25 to 50% having been reported. Chlorphenamine appears to undergo considerable first-pass metabolism. About 70% of chlorphenamine in the circulation is bound to plasma proteins. There is wide inter individual variation in the pharmacokinetics of Chlorphenamine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorphenamine is widely distributed in the body, and enters the CNS. Chlorphenamine maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorphenamine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces. Duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters. More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children.

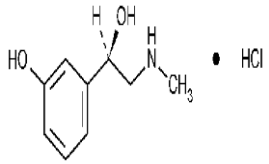
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

NA.

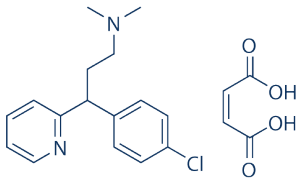
7. Description

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:



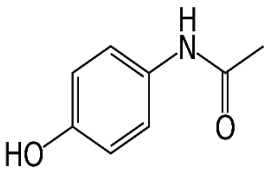
Its empirical formula is $C_9H_{13}NO_2$, and its molecular weight is 167.2 g/mol.

Chlorpheniramine maleate is in a class of medications called antihistamines. Its chemical name is(2Z)-but-2-enedioic acid; [3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl] dimethylamine and its structural formula is :



Its empirical formula is $C_{16}H_{19}ClN_2.C_4H_4O_4$ or $C_{20}H_{23}ClN_2O_4$and its molecular weight is 390.9.

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

36 months.

8.3 Packaging Information

15 tablets per strip of Sinarest New tablet.

8.4 Storage and handling instructions

Store below 30 ^{o}C 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 isadvised 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.

11. Details of permission or license number with date-158(472)/MFG/DFDA/2016/5802 dated. 28.03.2016 for domestic use. DCGI NOC Dated 05.03.2021.

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