Sinarest® Plus
Tablets

1. Generic Name

Paracetamol, Caffeine Anhydrous, Phenylephrine HCl and Chlorpheniramine Maleate tablets.

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:

Paracetamol IP ..... 650 mg

Caffeine Anhydrous IP ..... 30 mg

Phenylephrine HCl IP ..... 10 mg

Chlorpheniramine Maleate IP ..... 2 mg

Excipients ..... q.s.

Colour: Sunset Yellow FCF

3. Dosage form and Strength

Dosage: Sinarest Plus Tablets is available in oral dosage form.

Strength: Sinarest Plus Tablets is a Fixed Dose Combination of Paracetamol 650 mg, Caffeine 30 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 2 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

Sinarest Plus Tablets is indicated for the treatment of Common cold.

4.2 Posology and Method of Administration

Posology: For Adults the usual recommended dose is One Tablet thrice a day at 8 hourly intervals.

Method of Administration: Oral

4.3 Contraindication

Paracetamol: Contraindicated in hypersensitivity to any of the ingredients. Severe liver disease.

Phenylephrine HCl: Contraindicated in patients hypersensitive to any of the ingredients. Contraindicated in most types of cardiovascular disease, including angina and hypertension, and also in hyperthyroidism, hyperexcitability, phaeochromocytoma and closed angle glaucoma.

Chlorpheniramine Maleate: Contraindicated in Hypersensitivity to antihistamines; narrow-angle glaucoma; stenosing peptic ulcer; symptomatic prostatic hypertrophy; asthmatic attack; bladder neck obstruction; pyloroduodenal obstruction.

Caffeine: Contraindicated in patients with Porphyria

4.4 Special warnings and Precautions for use

Fixed dose combination shall not be used in children below four years of age.

Sinarest Plus Tablets should be used with caution in

- Elderly patients.
- patients with hyperthyroidism, myocardial disease, bradycardia, partial heart block or severe arteriosclerosis as it contains Phenylephrine.
- patients with asthma, bladder neck obstruction, , COPD, GI obstruction, glaucoma, hepatic impairment, hyperthyroidism, increased intraocular pressure, malnutrition, renal impairment, elderly patients and patients taking CNS depressants.
- patients suffering from cardiovascular diseases.

- patients who are suffering with severe hypovolemia as it contains Paracetamol.
- 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.
- 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 Plus Tablets to avoid dosing errors which could result in accidental overdose and death.
- Sinarest Plus Tablets contains Paracetamol which is 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 use of Paracetamol at doses that exceed the maximum daily limits and often involve more than one paracetamol-containing product.

Warning- Taking more than daily dose may cause serious liver damage or allergic reactions such as swelling of the face, mouth and throat, difficulty in breathing, itching and rash.

4.5 Drug Interactions

Paracetamol

- Anticoagulant drugs (warfarin) - dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.
- Paracetamol absorption gets increased by substances that increases gastric emptying, e.g. metoclopramide.
- Paracetamol absorption is decreased by substances that decreases gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic Analgesics.
- The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents
- Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.
- Colestyramine reduces the absorption of Paracetamol if given within 1 hour of Paracetamol.

Caffeine

- Drugs Metabolized by Cytochrome P450 1A2: Cytochrome P450 1A2 (CYP1A2) is known to be the major enzyme involved in the metabolism of caffeine. Therefore, caffeine has the potential to interact with drugs that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2. Lower doses of caffeine may be needed following coadministration of drugs which are reported to decrease caffeine elimination (e.g., cimetidine and ketoconazole) and higher caffeine doses may be needed following coadministration of drugs that increase caffeine elimination (e.g., phenobarbital and phenytoin). Caffeine may also increase the metabolism of other drugs such as phenobarbital and aspirin.
- Ephedrine: Caffeine and ephedrine are both CNS stimulant drugs. Co-administration of caffeine with ephedrine might cause too much stimulation and sometimes serious side effects and heart problems. Do not administer caffeine-containing products and ephedrine at the same time.

- Theophylline: Caffeine works similar to theophylline. Inter-conversion between caffeine and theophylline has been reported. Caffeine may decrease metabolism and excretion of theophylline and thus, might increase the effects and side effects of theophylline. The concurrent use of these drugs is not recommended.
- Beta-Adrenergic Agonists: Caffeine may enhance the cardiac inotropic effects of betaadrenergic stimulating agents. Co-administration of caffeine with these drugs should be avoided, as it might cause serious problems including increased heart rate and high blood pressure.
- Disulfiram: Co-administration of caffeine and disulfiram may lead to a substantial decrease in caffeine clearance. Co-administration of caffeine with disulfiram might increase the effects and side effects of caffeine including jitteriness, hyperactivity, and irritability.
- Quinolone Antibiotics: Caffeine accumulation may occur when products or foods containing caffeine are consumed concomitantly with quinolones such as ciprofloxacin. Co-administration of these antibiotics with caffeine can increase the risk of side effects including jitteriness, headache, increased heart rate, and other side effects.

Chlorpheniramine Maleate

- Chlorpheniramine Maleate taken with CNS depressants may cause increased sedation.
- Chlorpheniramine Maleate taken with MAO inhibitors causes increased anticholinergic effects.
- Chlorpheniramine Maleate inhibits phenytoin metabolism and can lead to phenytoin toxicity.

Phenylephrine Hydrochloride

- Phenylephrine can interact with Monoamine Oxidase Inhibitors (MAOIs) or tricyclic antidepressants and an indirect or mixed-acting sympathomimetic and may result in a hypertensive crisis.
- Concomitant use of Phenylephrine with Digoxin or cardiac glycosides may increase the risk of irregular heartbeat or heart attack.

4.6 Use in Special Population

- **Paediatric:** No data available. If used use with caution under medical supervision. (Fixed dose combination shall not be used in children below four 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 LP New Tablet is recommended to be taken during pregnancy only under doctor's recommendation.

4.7 Effects on ability to drive and use machines

It is advisable not to drive or operate machinery when on treatment with Sinarest Plus Tablets.

4.8 Undesirable Effects:

Paracetamol

Paracetamol has reported to show Fixed Drug Eruptions. It is safe as well as well tolerated drug and suspected adverse drug reaction are very rare and of mild intensity which are nausea, rashes or leukopenia. In very rare cases serious, adverse drug reaction may occur including rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing, Fixed Drug Eruption.

Caffeine

Caffeine may cause CNS adverse effects such as insomnia, dizziness, restlessness, excitability, anxiety, irritability, nervousness and mild delirium. Caffeine may also cause

gastrointestinal adverse effects such as nausea, vomiting and gastric irritation. High doses of caffeine can cause tremors and palpitations.

Phenylephrine Hydrochloride

Oral Phenylephrine Hydrochloride may cause mild upset stomach, trouble sleeping, dizziness, light headedness, nervousness, shaking, dry mouth or fast heartbeat, high blood pressure with headache.

Chlorpheniramine Maleate

CNS: stimulation, sedation, drowsiness, excitability; CV: hypotension, palpitations, weak pulse; GI: epigastric distress, dry mouth, constipation; GU: urine retention; Respiratory: thick bronchial secretions.

4.9 Overdose

Initiate general symptomatic and supportive measures in all cases of overdosages where necessary as directed by the physician.

5. Pharmacological properties

5.1 Mechanism of Action Paracetamol:

Paracetamol acts primarily in the CNS, increases 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 centers of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation.

Caffeine:

Central Nervous system stimulant: It stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines.

Analgesic Adjunct: Caffeine constricts cerebral vasculature with an accompanying decrease in the cerebral blood flow and in the oxygen tension of the brain. It is believed

that caffeine helps to relieve headaches by providing more rapid onset of action and/or enhanced pain relief with lower doses of analgesic.

Phenylephrine hydrochloride:

Phenylephrine is indicated for symptomatic relief from nasal congestion caused by the common cold. As a vasoconstrictor, Phenylephrine possesses both indirect and direct sympathomimetic effects. The dominant, direct effect is agonism at α1-adrenergic receptors located on capacitance blood vessels of the nasal mucosa, resulting in vasoconstriction, which limits the amount of fluid to enter the nose, throat, and sinus linings, and decreases inflammation of nasal membranes.

Chlorpheniramine maleate:

Chlorpheniramine is a histamine H1 antagonist (or more correctly, an inverse histamine agonist) 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.

5.2 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. 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.

Caffeine is a CNS stimulating agent. Caffeine produces wakefulness and increases mental activity/ alertness.

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. 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 (N-acetyl 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.

Caffeine: After oral administration, caffeine is completely and rapidly absorbed with peak plasma concentrations occurring between 5 and 90 minutes (in fasting state). There is no evidence of pre-systemic metabolism. Caffeine distributes into all body fluids. The mean plasma protein binding of caffeine is 35%. Caffeine is metabolised almost completely via

oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine). Minor metabolites include 1-methylacrylic acid and 5-acetylamine-6-formylamine-3methyluracil (AFMU). In adults, elimination is almost entirely by hepatic metabolism. Marked individual variability occurs in the rate of elimination. The mean plasma elimination half-life is 4.9 hours, with a range of 1.9 to 12.2 hours.

Phenylephrine has low oral bioavailability owing to irregular absorption and first-pass metabolism by monoamine oxidase in the gut and liver. It retains activity as a nasal decongestant when given orally, the drug distributing through the systemic circulation to vascular bed of the nasal mucosa. When taken by mouth as a nasal decongestant phenylephrine is usually given at intervals of 4-6 hrs.

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.

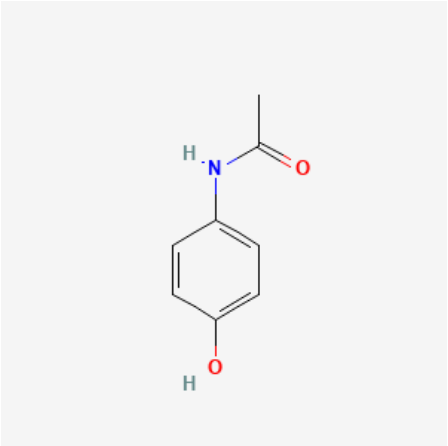
6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

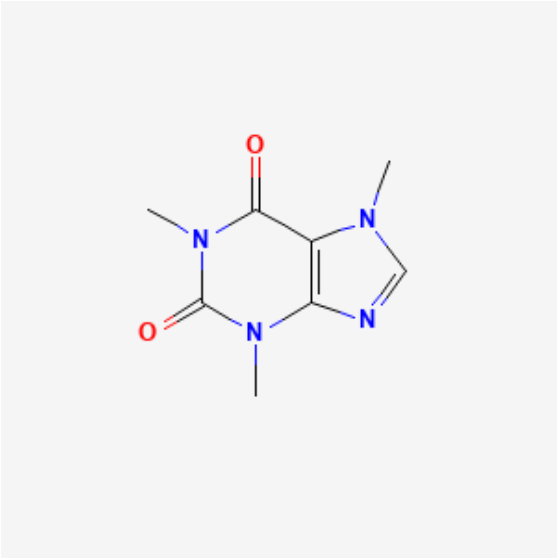
NA

7. Description

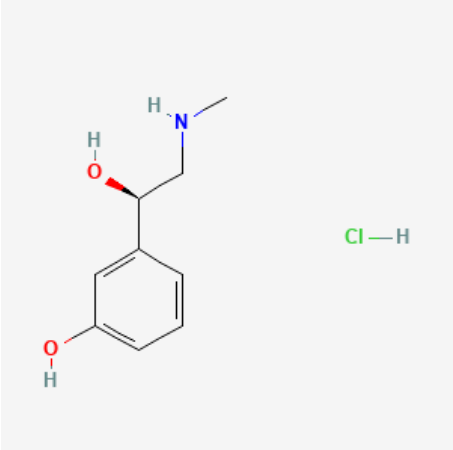
Paracetamol belongs to Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Its chemical name is *N*-(4-hydroxyphenyl) acetamide. Its empirical formula is $C_8H_9NO_2$ and its molecular weight is 151.16 g/mol. Its structural formula is:



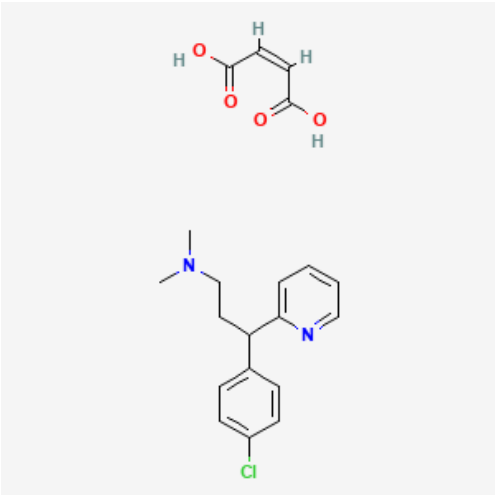
Caffeine is a methylxanthine alkaloid that occurs naturally in seeds, leaves and fruit of several plants. Its chemical name is 1,3,7-trimethylpurine-2,6-dione, its empirical formula is $C_8H_{10}N_4O_2$, and its molecular weight is 194.19 g/mol. Its structural formula is:



Phenylephrine Hydrochloride is in a class of medications called direct acting sympathomimetic amine (nasal decongestants). Its chemical name is 3-[(1R)-1-hydroxy-2-(methylamino)ethyl]phenol; hydrochloride. Its empirical formula is $C_9H_{14}ClNO_2$, and its molecular weight is 203.66 g/mol. Its structural formula is:



Chlorpheniramine Maleate is in a class of medications called antihistamines. Its chemical name is (Z)-but-2-enedioic acid;3-(4-chlorophenyl)-N,N-dimethyl-3-pyridin-2-ylpropan-1-amine. Its empirical formula is $C_{20}H_{23}ClN_2O_4$ and its molecular weight is 390.9 g/mol. Its structural formula is:



8. Pharmaceuticals Particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf life

24 months

8.3 Packaging Information

20 tablets per strip of Sinarest Plus Tablets.

8.4 Storage and Handling Instructions

Do not freeze, protect from direct sunlight and moisture at a temperature not exceeding 30°C.

Keep the medicine out of reach of children.

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 adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by

Dallas Drugs Pvt Ltd

11. Details of Permission or license number with date

MNB/19/1088 & MB/19/1089; Dated - 25/10/2019

12. Date of Revision: September 2026