Sinarest®
Oral Drops

1. Generic Name
Sinarest Oral Drops is a fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml.

2. Qualitative and Quantitative composition
Each ml contains

Paracetamol	125 mg
Phenylephrine Hydrochloride	2.5 mg
Chlorpheniramine maleate	1 mg

3. Dosage form and strength
Dosage : Sinarest Oral Drop is available in oral dosage form.
Strength : Sinarest Oral drops is a fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml.

4. Clinical particulars

4.1 Therapeutic indication
Sinarest Oral Drops is indicated for the symptomatic treatment of common cold in infants.

4.2 Posology and method of administration
Sinarest Oral Drops should be taken as directed by physician or as mentioned in the table given below.

Weight in Kg	Age in months	Dose
2.5 – 9.7 kg	1-6 months	0.2 ml tid / qid
6.7 – 11.8 kg	7-12 months	0.2 – 0.4 ml tid / qid

Method of administration for Sinarest Oral Drops is oral administration.

4.3 Contraindication
The use of Sinarest Oral Drops is contraindicated in:
- Patients hypersensitive to Paracetamol, Phenylephrine and Chlorpheniramine or any other excipients present in Sinarest Oral Drops.
- Patients with severe hypertension
- Patients who are on MAO inhibitors
- Patients with hepatic impairment, severe renal failure or closed angle glaucoma.

4.4 Special warnings and precautions for use
- Sinarest Oral Drops should be used with caution in elderly patients.
- Sinarest Oral Drops should be used with caution in patients with hyperthyroidism, myocardial disease, bradycardia, partial heart block or severe arteriosclerosis as it contains Phenylephrine.
- Sinarest Oral Drops should be used with caution in patients with 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.
- Sinarest Oral Drops should be used with caution in 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.

- It is advisable not to drive or operate machinery when on treatment with Sinarest Oral Drops.
- 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 and raised intra-ocular pressure including glaucoma; prostatic hypertrophy; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis or asthma; hepatic impairment; renal impairment.
- Patients who are more likely to experience the neurological anticholinergic effects and paradoxical excitation (eg. increased energy, restlessness or nervousness) should not use with other antihistamine containing products, including 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 Oral Drops to avoid dosing errors which could result in accidental overdose and death.
- Sinarest Oral Drops 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 the use of Paracetamol at doses that exceed the maximum daily limits, and often involve more than one Paracetamol-containing product.

Box 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

Below mentioned are the drug- drug interactions of 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.
- Cholestyramine reduces the absorption of Paracetamol if given within 1 hour of Paracetamol.

Below mentioned are the drug- drug interactions of Chlorpheniramine Maleate:

- Drug-drug interactions of Chlorpheniramine Maleate may occur with CNS depressants as it may cause increased sedation.
- Drug-drug interactions of Chlorpheniramine Maleate may occur with MAO inhibitors as it cause increased anticholinergic effects.

The below mentioned drug- drug interactions of Phenylephrine Hydrochloride have been noted:

- Drug-drug interactions of Phenylephrine may occur with Monoamine Oxidase Inhibitors (MAOIs) or tricyclic antidepressants and an indirect or mixed-acting Sympathomimetic and may result in a hypertensive crisis.

4.6 Use in special population

- Pediatric: safe
- 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 Oral Drops 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 Oral Drops.

4.8 Undesirable effects

Below mentioned are the suspected adverse drug reactions of Paracetamol, Phenylephrine and Chlorpheniramine Maleate.
Below mentioned is the summary of adverse drug reactions which may occur due to Paracetamol:
Paracetamol 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 and trouble breathing.

Below mentioned is the summary of adverse drug reaction which may occur due to Phenylephrine:
Oral Phenylephrine hydrochloride may cause mild upset stomach, trouble sleeping, dizziness, light-headedness, headache, nervousness, shaking, dry mouth or fast heartbeat.

Below mentioned are the adverse drug reaction may occur due to 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 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.

Phenylephrine is indicated for the 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, results in vasoconstriction, which limits the amount of fluid to enter the nose, throat, and sinus linings, and decreases inflammation of nasal membranes.

Chlorpheniramine maleate is a histamine H1 antagonist used in allergic reactions, hay fever, rhinitis, urticaria and asthma. The mechanism of action of Chlorpheniramine maleate is, it binds to the histamine H1 receptor. This blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine. 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. 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. Parentral 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 (Nacetylp-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.

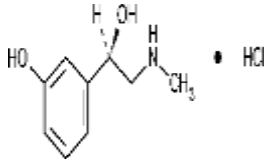
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

NA.

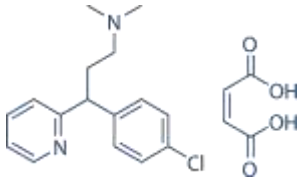
7. Description

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:



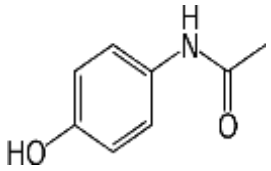
Its empirical formula is $C_9H_{13}NO_2$, and its molecular weight is 167.2 g/mol.

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

Sinarest Oral Drops are available in 15 ml bottle.

8.4 Storage and handling instructions

Store below 30 ^{o}C in a dark place and do not freeze it.

9. Patient Counselling Information

9.1 Adverse Reactions

Sinarest Oral Drops is generally well tolerated and adverse drug reactions are rare. Sinarest Oral Drops contains Paracetamol, Phenylephrine and Chlorpheniramine Maleate. Below we have mentioned the adverse drug reactions of Paracetamol, Phenylephrine and Chlorpheniramine Maleate.

Below mentioned is the summary of adverse drug reactions which may occur due to Paracetamol.
Paracetamol 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 and trouble breathing.

Below mentioned is the summary of adverse drug reaction which may occur due to Phenylephrine.
Oral Phenylephrine hydrochloride may cause mild upset stomach, trouble sleeping, dizziness, lightheadedness, headache, nervousness, shaking, dry mouth or fast heartbeat.

Below mentioned are the adverse drug reaction may occur due to 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.

9.2 Drug Interactions

The below mentioned are the drug- drug interactions of 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

Below mentioned drug- drug interactions of Chlorpheniramine Maleate:

- Drug-drug interactions of Chlorpheniramine Maleate may occur with CNS depressants as it may cause increased sedation.
- Drug-drug interactions of Chlorpheniramine Maleate may occur with MAO inhibitors as it causes increased anticholinergic effects.

Below mentioned drug- drug interactions of Phenylephrine Hydrochloride:

Drug-drug interactions of Phenylephrine may occur with Monoamine Oxidase Inhibitors (MAOIs) or tricyclic antidepressants and an indirect or mixed-acting sympathomimetic and may result in a hypertensive crisis.

9.3 Dosage

Sinarest Oral Drops should be taken as directed by physician or as mentioned in the table below.

Weight in Kg	Age in months	Dose
2.5 – 9.7 kg	1-6 months	0.2 ml tid / qid
6.7 – 11.8 kg	7-12 months	0.2 – 0.4 ml tid / qid

9.4 Storage

Store below 30 ^{o}C in a dark place and do not freeze it.

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

Guardian of the patient (as patient is of age below 1 year) is advised to be alert for the emergence or worsening of the adverse event and should contact the prescribing physician.

9.8 Contraindications

The use of Sinarest Oral Drops is contraindicated in:

- Patients hypersensitive to Paracetamol, Phenylephrine and Chlorpheniramine Maleate or any other excipients present in Sinarest Oral Drops
- Patients with severe hypertension.
- Patients who are on MAO inhibitors.
- Patients with hepatic impairment, severe renal failure or closed angle glaucoma.

10. Manufactured by

Centaur Pharmaceuticals Pvt. Ltd., Lab Daffodil and Goa Antibiotics.

11. Details of permission or license number with date

23rd August 2021 (As per the NOC received from DCGI, letter dated 23-08-21, file no. FDC/MA/21/000163 after filling the form CT- 21 dated 23-07-2021).

12. Date of revision: July 2021