Sinarest®

Oral Drops

1. Composition

Paracetamol	125mg
Phenylephrine	2.5 mg
Chlorpheniramine maleate	1mg

2. Dosage form and strength

Sinarest Oral Drops is available in 15 ml bottle with a calibrated dropper.

3. Clinical particulars

3.1 Therapeutic indication

Sinarest Oral Drops is indicated for:

- Relief of nasal and sinus congestion.
- Relief of allergic symptoms of the nose or throat due to upper respiratory tract allergies.
- Relief of sinus pain and headache.
- Adjunct with antibacterials in sinusitis, tonsillitis and otitis media.

3.2 Posology and method of administration

The usual recommended oral dose of Sinarest Oral Drops in infants is as follows:

1-6 months= 0.2 ml thrice/four times a day.

7-12 months= 0.2-0.4 ml thrice/four times a day.

1-2 years= 0.4-0.8 ml thrice/four times a day.

3.3 Contraindication

The use of Sinarest Oral Drops is contraindicated in patients with:

- Hypersensitivity to any of the ingredients of the formulation.
- Severe hypertension.

3.4 Special warnings and precautions for use

- In case a hypersensitivity reaction occurs which is rare, Sinarest Oral Drops should be discontinued.
- Sinarest Oral Drops contains Paracetamol and therefore should not be used in conjunction with other Paracetamol containing products.
- Sinarest Oral Drops should be used with caution in patients with renal or hepatic dysfunction, diabetes mellitus, hyperthyroidism, cardiovascular problems, epilepsy and closed angle glaucoma.

3.5 Drug interactions

Clinically significant drug interactions may occur on concomitant administration of Sinarest Oral Drops with monoamine oxidase inhibitors, tricyclic antidepressants, beta-adrenergic agents, and methyldopa, reserpine and veratrum alkaloids.

3.6 Use in special population

- Pediatric: Safe.
- 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: 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.

3.7 Effects on ability to drive and use machine

Chlorpheniramine in Sinarest Oral Drops may cause sedation. It is advisable not to drive or operate machinery when on treatment with Sinarest Oral Drops.

3.8 Undesirable effects

Sinarest Oral Drops is generally well tolerated and adverse events are rare. Hypersensitive individuals may display ephedrine-like reactions such as tachycardia, palpitations, headache, dizziness and nausea. Use of sympathomimetics has been associated with fear, anxiety, restlessness, tremor, weakness, dysuria, insomnia, hallucinations and convulsions. Chlorpheniramine in Sinarest Oral Drops may cause sedation.

3.9 Overdose

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

4. Pharmacological properties

4.1 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 α1-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 H1-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.

4.2 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.

4.3 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.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

36 months.

7.3 Storage and handling instructions

Store below 30 ^{o}C in a dark and dry place.