Sinarest® FxP TABLETS

Composition:

Each Sinarest FxP Tablet contains:

Paracetamol	500 mg
Fexofenadine	60 mg
Phenylephrine	10 mg

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.

Fexofenadine is rapidly absorbed after oral doses with peak plasma concentrations being reached in 2 to 3 hours. It is about 60 to 70% bound to plasma proteins. About 5% of the total dose is metabolised, mostly by the intestinal mucosa, with only 0.5 to 1.5% of the dose undergoing hepatic biotransformation by the cytochrome P450 system. Elimination half-life of about 14 hours has been reported although this may be prolonged in patients with renal impairment. Excretion is mainly in the faeces with only 10% being present in the urine. Fexofenadine does not appear to cross the blood brain barrier. Fexofenadine is a metabolite of terfenadine and as such has been detected in breast milk after the administration of terfenadine.

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.

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.

Like other H1-blockers, Fexofenadine competes with free histamine for binding at H1-receptors in the GI tract, large blood vessels, and bronchial smooth muscle. This block the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms (eg. nasal congestion, watery eyes) brought on by histamine. Fexofenadine exhibits no anticholinergic, antidopaminergic, alpha1-adrenergic or beta-adrenergic-receptor blocking effects.

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.

Other 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.

Fexofenadine is a second-generation, long lasting H1-receptor antagonist (antihistamine) which has a selective and peripheral H1-antagonist action. Histamine is a chemical that causes many of the signs that are part of allergic reactions, such as the swelling of tissues. Histamine is released from histamine-storing cells (mast cells) and attaches to other cells that have receptors for histamine. The attachment of the histamine to the receptors causes the cell to be "activated," releasing other chemicals which produce the effects that we

associate with allergy. Fexofenadine blocks one type of receptor for histamine (the H1 receptor) and thus prevents activation of cells by histamine. Unlike most other antihistamines, Fexofenadine does not enter the brain from the blood and, therefore, does not cause drowsiness. Fexofenadine lacks the cardiotoxic potential of terfenadine, since it does not block the potassium channel involved in repolarization of cardiac cells.

Phenylephrine is a powerful vasoconstrictor. It is used as a nasal decongestant and cardiotonic agent. Phenylephrine is a postsynaptic α_1-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.

Indication:

Sinarest FxP Tablet is indicated in

- Rhinopharyngitis
- Rhinitis with Deviated Nasal Symptoms
- Tonsillitis

Contraindication:

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

- Hypersensitivity to any ingredient in this product.
- Severe hepatic dysfunction.

Drug Interaction:

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

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 Cholestyramine reduces the absorption of paracetamol if given within 1 hour.
- Regular use of paracetamol possibly reduces metabolism of Zidovudine (increased risk of neutropenia).

Adverse effects:

Sinarest FxP Tablet is well tolerated. Side effects are mild and often transient.

- Fexofenadine: Headache, otitis media, vomiting.
- Phenylephrine: As a class, sympathomimetic amines may also cause headaches, vomiting, diarrhea, insomnia, restlessness and palpitations. However, there have been few reports of these with normal doses of Phenylephrine.
- Paracetamol rarely causes any problems but allergic reactions, such as skin rash, occasionally occur. There have been very rare reports of blood disorders but these were not necessarily caused by paracetamol.

Warnings and Precautions:

- In case a hypersensitivity reaction occurs which is rare, SINAREST FxP Tablet should be discontinued.
- SINAREST FxP Tablet contains Paracetamol and therefore should not be used in conjunction with other Paracetamol containing products.
- SINAREST FxP Tablet should be used with caution in patients with renal or hepatic dysfunction, diabetes mellitus, hyperthyroidism, cardiovascular problems, epilepsy and closed angle glaucoma.
- It is advisable not to drive or operate machinery when on treatment with SINAREST FxP Tablet.
- Antacids containing aluminium and magnesium hydroxide reduce the absorption of fexofenadine. Fruit juices including grapefruit may reduce the bioavailability of fexofenadine and use together should be avoided.

Use in special population:

1. **Pediatric:** Use with caution.
2. **Geriatric:** Elderly population may be at greater risk for the side-effects.
3. **Liver impairment:** Use with caution.
4. **Renal failure:** Use with caution.
5. **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 syrup should be used during pregnancy

only if clearly needed. No adverse effects have been seen in breastfed infants whose mothers were receiving fexofenadine and therefore usually compatible with breast feeding.

Dosage:

Adults: The usual recommended dose is 1 tablet twice a day.

Presentation:

Sinarest FxP Tablets are available in blister strips of 10 tablets.

Storage and handling:

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