XADINE PLUS
(Fexofenadine HCl U.S.P. + Pseudoephedrine HCl B.P.)

60mg + 60 mg

Tablets

COMPOSITION

Each film-coated tablet contains:
Fexofenadine hydrochloride U.S.P. 60mg
Pseudoephedrine HCl B.P. …… 60 mg

THERAPEUTIC INDICATIONS

Adults and children 12 years of age and over:
Fexofenadine HCl/Pseudoephedrine HCl tablet is indicated for: • the effective relief of sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes, and temporary relief of nasal congestion associated with seasonal allergic rhinitis;
• patients who may not receive complete relief from antihistamines alone and in whom both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired.

Geriatrics (> 65 years of age):
The elderly are more likely to have adverse reactions to sympathomimetic amines. Therefore, use of Fexofenadine HCl/Pseudoephedrine HCl tablet in this population should be discussed with a doctor before use.

Pediatrics (< 12 years of age):
Fexofenadine HCl/Pseudoephedrine HCl tablet is not indicated for children < 12 years of age.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adults and Children 12 years of age and older

One Fexofenadine HCl/Pseudoephedrine HCl tablet twice daily, swallowed whole on an empty stomach.

Children under 12 years of age

Safety and effectiveness of Fexofenadine HCl/Pseudoephedrine HCl tablet have not been established in this population. Therefore, use of Fexofenadine HCl/Pseudoephedrine HCl tablet in this population is not recommended.

Geriatrics (> 65 years of age):

The elderly is more likely to have adverse reactions to sympathomimetic amines. Therefore, use of Fexofenadine HCl/Pseudoephedrine HCl tablet in this population should be discussed with a doctor before use. Use in renal impairment A dose of one caplet once daily is recommended as a starting dose.

Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount. Two doses should not be taken at the same time.

CONTRAINDICATIONS

Fexofenadine HCl/Pseudoephedrine HCl tablet is contraindicated in patients with known hypersensitivity or idiosyncrasy to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container, to adrenergic agents or to other drugs of similar chemical structures.

Fexofenadine HCl/Pseudoephedrine HCl tablet is also contraindicated in the following patients:

• patients with severe hypertension, or severe coronary artery disease, narrow-angle glaucoma or urinary retention.

• patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment.

• patients who have shown sensitivity to adrenergic agents (manifestations include insomnia, dizziness, weakness, tremor, or arrhythmias).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Sympathomimetics should be used with caution in patients receiving digitalis. Sympathomimetics may cause central nervous system (CNS) stimulation and convulsions or cardiovascular collapse with accompanying hypotension.

Carcinogenesis and Mutagenesis

No human data available

Cardiovascular

Fexofenadine HCl/Pseudoephedrine HCl tablet should be used with caution in patients with hypertension, ischemic heart disease. Pseudoephedrine, like other sympathomimetic amines, may produce cardiovascular collapse.

Dependence/Tolerance

There are no data available to indicate that abuse or dependency occurs with Fexofenadine HCl /Pseudoephedrine HCl tablet.

Endocrine and Metabolism

Fexofenadine HCl/Pseudoephedrine HCl tablet should be used with caution in patients with diabetes mellitus, hyperthyroidism.

Genitourinary

Fexofenadine HCl/Pseudoephedrine HCl tablet should be used with caution in patients with prostatic hypertrophy.

Neurologic

Pseudoephedrine, like other sympathomimetic amines, may produce central nervous system stimulation with convulsions. Fexofenadine HCl/Pseudoephedrine HCl tablet should be used with caution in patients with hyperreactivity to ephedrine.

Ophthalmologic

Fexofenadine HCl/Pseudoephedrine HCl tablet should be used with caution in patients with increased intraocular pressure.

Renal

Fexofenadine HCl/Pseudoephedrine HCl tablet should be used with caution in patients with renal impairment. Patients with decreased renal function should be given a lower initial dose, one caplet per day, due to the reduced elimination of fexofenadine and pseudoephedrine.

Special Populations

Pregnant Women: There are no adequate and well controlled studies in pregnant women. Fexofenadine HCl/Pseudoephedrine HCl tablet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: Fexofenadine HCl/Pseudoephedrine HCl tablet is not recommended for nursing women unless the potential benefit to the patient outweighs the potential risk to the infant. Following administration of terfenadine to nursing mothers, fexofenadine crosses into human breast milk and pseudoephedrine administered alone, distributes into breast milk.

Pediatrics (< 12 years of age): Safety and effectiveness of Fexofenadine HCl/Pseudoephedrine HCl tablet have not been established in children under 12 years of age.

Geriatrics (> 65 years of age): The elderly are more likely to have adverse reactions to sympathomimetic amines. Therefore, use of Fexofenadine HCl/Pseudoephedrine HCl tablet in this population should be discussed with a doctor before use.

DRUG INTERACTIONS

Drug-Drug Interactions

Fexofenadine HCl has no effect on the pharmacokinetics of erythromycin and ketoconazole. The coadministration of fexofenadine hydrochloride with erythromycin or ketoconazole resulted in no significant increases in QTc. No differences in adverse effects were reported whether this agent was administered alone or in combination with erythromycin or ketoconazole. Since fexofenadine HCl does not undergo hepatic biotransformation, it is unlikely to interact with drugs that rely upon hepatic metabolism.

The administration of a single 20 mL dose of antacid followed 15 min later by a single oral dose of 120 mg fexofenadine HCl resulted in a significant reduction in fexofenadine bioavailability (41% reduction in AUC (0-30h); 43% reduction in Cmax). This interaction has been explained on the basis that up to 27.8% of fexofenadine is physically bound to antacid in the stomach at pH of 4 or greater.

Concomitant use of pseudoephedrine with monoamine oxidase (MAO) inhibitors and use within 14 days after stopping an MAO inhibitor is contraindicated.

Concomitant use of pseudoephedrine with antihypertensive drugs which interfere with sympathetic activity may reduce their antihypertensive effects. Concomitant use of pseudoephedrine with sympathomimetic agents may have additive cardiovascular effects.

Drug-Food Interactions

Interactions with food have not been established. Or Co-administration of Fexofenadine HCl/Pseudoephedrine HCl tablet with a high fat meal decreased fexofenadine bioavailability; however, the rate or extent of pseudoephedrine absorption was not affected.

Fexofenadine HCl/Pseudoephedrine HCl tablet should be taken on an empty stomach.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Laboratory Tests Interactions

Fexofenadine HCl /Pseudoephedrine HCl tablet should be discontinued approximately 3 days prior to skin testing procedures since antihistamines may prevent or diminish otherwise positive reactions to dermal reactivity indications.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Teratogenic Effects

Category C. Terfenadine alone was not teratogenic in rats and rabbits at oral doses up to 300 mg/kg; 300 mg/kg of terfenadine produced fexofenadine AUC values that were approximately 4 and 30 times, respectively, the AUC at the maximum recommended human daily oral dose of Fexofenadine HCl /pseudoephedrine HCl tablet.

In mice, no adverse effects and no teratogenic effects during gestation were observed with fexofenadine at dietary doses up to 3730 mg/kg (approximately 15 times the maximum recommended human daily oral dose of Fexofenadine HCl/Pseudoephedrine HCl tablet based on comparison of the AUCs).

The combination of terfenadine and pseudoephedrine hydrochloride in a ratio of 1:2 by weight was studied in rats and rabbits. In rats, an oral combination dose of 150/300 mg/kg produced reduced fetal weight and delayed ossification with a finding of wavy ribs. The dose of 150 mg/kg of terfenadine in rats produced an AUC value of fexofenadine that was approximately 4 times the AUC at the maximum recommended human daily oral dose of Fexofenadine HCl 60 mg/pseudoephedrine HCl 60 mg tablet. The dose of 300 mg/kg of pseudoephedrine hydrochloride in rats was approximately 10 times the maximum recommended human daily oral dose of Fexofenadine HCl/Pseudoephedrine HCl tablet HOUR on a mg/m^2 basis. In rabbits, an oral combination dose of 100/200 mg/kg produced decreased fetal weight. By extrapolation, the AUC of fexofenadine for 100 mg/kg orally of terfenadine was approximately 10 times the AUC at the maximum recommended human daily oral dose of Fexofenadine HCl 60 mg/pseudoephedrine HCl 60 mg tablet. The dose of 200 mg/kg of pseudoephedrine hydrochloride was approximately 15 times the maximum recommended human daily oral dose of Fexofenadine HCl/Pseudoephedrine HCl tablet on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Fexofenadine HCl/Pseudoephedrine HCl tablet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Dose-related decreases in pup weight gain and survival were observed in rats exposed to an oral dose of 150 mg/kg of terfenadine; this dose produced an AUC of fexofenadine that was approximately 4 times the AUC at the maximum recommended human daily oral dose of Fexofenadine HCl 60 mg/pseudoephedrine HCl 60 mg tablet.

Nursing Mothers

It is not known if fexofenadine is excreted in human milk. Because many drugs are excreted in human milk, caution should be used when fexofenadine hydrochloride is administered to a nursing woman. Pseudoephedrine hydrochloride administered alone distributes into breast milk of lactating human females. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by AUC is 2 to 3 times greater than the plasma AUC. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to 0.7%. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when Fexofenadine HCl/Pseudoephedrine HCl tablet is administered to nursing women

ADVERSE DRUG REACTIONS

Combination of Fexofenadine hydrochloride/ Pseudoephedrine hydrochloride

In one clinical trial (n=651) in which 215 subjects with seasonal allergic rhinitis received the 60 mg fexofenadine hydrochloride/120 mg pseudoephedrine hydrochloride combination tablet twice daily for up to 2 weeks, adverse events were similar to those reported either in subjects receiving fexofenadine hydrochloride 60 mg alone (n=218 subjects) or in subjects receiving pseudoephedrine hydrochloride 120 mg alone (n=218). A placebo group was not included in this study.

The percent of subjects who withdrew prematurely because of adverse events was 3.7% for the fexofenadine hydrochloride/pseudoephedrine hydrochloride combination group, 0.5% for the fexofenadine hydrochloride group, and 4.1% for the pseudoephedrine hydrochloride group. All adverse events that were reported by greater than 1% of subjects who received the recommended daily dose of the fexofenadine hydrochloride/pseudoephedrine hydrochloride combination are listed in the following table.

Adverse Experiences Reported in One Active-Controlled Seasonal Allergic Rhinitis Clinical Trial at Rates of Greater than 1%

Adverse Experience	**60 mg Fexofenadine Hydrochloride/120 mg Pseudoephedrine Hydrochloride Combination Tablet Twice Daily (n=215)**	**Fexofenadine Hydrochloride 60 mg Twice Daily (n=218)**	**Pseudoephedrine Hydrochloride 120 mg Twice Daily (n=218)**
Headache	13.0%	11.5%	17.4%
Insomnia	12.6%	3.2%	13.3%
Nausea	7.4%	0.5%	5.0%
Dry Mouth	2.8%	0.5%	5.5%
Dyspepsia	2.8%	0.5%	0.9%

Throat Irritation	2.3%	1.8%	0.5%
Dizziness	1.9%	0.0%	3.2%
Agitation	1.9%	0.0%	1.4%
Back Pain	1.9%	0.5%	0.5%
Palpitation	1.9%	0.0%	0.9%
Nervousness	1.4%	0.5%	1.8%
Anxiety	1.4%	0.0%	1.4%
Upper Respiratory Infection	1.4%	0.9%	0.9%
Abdominal Pain	1.4%	0.5%	0.5%

Many of the adverse events occurring in the fexofenadine hydrochloride/pseudoephedrine hydrochloride combination group were adverse events also reported predominately in the pseudoephedrine hydrochloride group, such as insomnia, headache, nausea, dry mouth, dizziness, agitation, nervousness, anxiety, and palpitation.

Fexofenadine Hydrochloride

In placebo-controlled clinical trials, which included 2461 subjects receiving fexofenadine hydrochloride at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated subjects. The incidence of adverse events, including drowsiness, was not dose related and was similar across subgroups defined by age, gender, and race. The percent of subjects who withdrew prematurely because of adverse events was 2.2% with fexofenadine hydrochloride vs 3.3% with placebo.

Events that have been reported during controlled clinical trials involving subjects with seasonal allergic rhinitis and chronic idiopathic urticaria at incidences less than 1% and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or paroniria. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

Pseudoephedrine Hydrochloride

Pseudoephedrine hydrochloride may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, drowsiness, tachycardia, palpitation, pressor activity, cardiac arrhythmias and ischemic colitis have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

In the event of overdosage, treatment which should be started immediately, is symptomatic and supportive. Discontinuation of use, gastric lavage or induction of emesis (except in patients with impaired consciousness) and support of vital functions are advised.

Fexofenadine

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses up to 800 mg and doses up to 690 mg BID for one month or 240 mg QD for one year were studied in healthy subjects without the development of clinically significant adverse events as compared to placebo. The maximum tolerated dose of fexofenadine hydrochloride was not established.

Pseudoephedrine

Serious effects associated with pseudoephedrine overdosage include respiratory difficulty, convulsions, arrhythmias, hypertension and cardiovascular collapse. Manifestations These may vary from CNS depression (sedation, apnea, diminished mental alertness, cyanosis, coma, cardiovascular collapse) to stimulation (insomnia, hallucination, tremors or convulsions) to death. Other signs and symptoms may be euphoria, excitement, tachycardia, palpitations, thirst, perspiration, nausea, dizziness, tinnitus, ataxia, blurred vision and hypertension or hypotension. Stimulation is particularly likely in children, as are atropine-like signs and symptoms (dry mouth; fixed, dilated pupils; flushing; hyperthermia; and gastrointestinal symptoms). In large doses, sympathomimetics may give rise to giddiness, heachache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma and respiratory failure.

Treatment

The patient should be induced to vomit, even if emesis has occurred spontaneously. Pharmacologically-induced vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. The action of ipecac is facilitated by physical activity and by the administration of 240 to 360 milliliters of water. If emesis does not occur within 15 minutes, the dose of ipecac should be repeated. Precautions against aspiration must be taken, especially in children. Following emesis, adsorption of any drugs remaining in the stomach may be attempted by the administration of activated charcoal as a slurry with water. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed. Physiologic saline solution is the lavage solution of choice, particularly in children. In adults, tap water can be used; however, as much as possible of the amount administered should be removed before the next instillation. Saline cathartics draw water into the bowel by osmosis and therefore may be valuable for their action in rapid dilution of bowel content. Fexofenadine is not effectively cleared by hemodialysis from the blood. The effect of hemodialysis on pseudoephedrine is unknown. Excretion of pseudoephedrine is increased by lowering the pH of the urine. After emergency treatment, the patient should continue to be medically monitored. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or hypothermic blanket. Apnea is treated with ventilatory support.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of Action

Fexofenadine hydrochloride/ Pseudoephedrine hydrochloride Tablet is a combination product containing a nonsedating antihistamine with selective peripheral H1-receptor antagonist activity and an orally active sympathomimetic amine that exerts a decongestant action on the nasal mucosa.

Fexofenadine is the predominant human and animal active metabolite of terfenadine. Fexofenadine hydrochloride inhibits histamine induced skin wheal and flare responses. Following single and twice daily oral administration, antihistaminic effects occur within one hour, achieve a maximum at two to three hours, and last a minimum of 12 hours. There is no evidence of tolerance to these effects after 28 days of dosing.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine which exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. In randomized, double-blind, placebo-controlled trials, a daily dose of fexofenadine 60 mg b.i.d. was shown to be effective in relieving the symptoms of seasonal allergic rhinitis (trees and grasses in the spring or ragweed pollen in the fall). These symptoms consisted of sneezing, rhinorrhea, itchy nose/palate/throat and itchy, watery, red eyes. In a randomized, double-blind, parallel-design safety and efficacy study, a daily dose of fexofenadine HCl 60 mg/pseudoephedrine 120 mg

b.i.d. was more effective than the decongestant alone (pseudoephedrine 120 mg b.i.d.) for histamine-mediated symptoms of seasonal allergic rhinitis, and more effective than the antihistamine component alone (fexofenadine 60 mg b.i.d.) for the non-histamine-mediated symptoms of seasonal allergic rhinitis. Moreover, the combination therapy demonstrated higher improvement in the regular daily activities and work productivity than its components alone. There was no statistically significant difference in the treatment effect in subgroups defined by age, sex, race or weight.

Pharmacokinetics

Absorption:

Fexofenadine HCl + Pseudoephedrine HCl was rapidly absorbed following multiple dose administration of the 60 mg fexofenadine hydrochloride/120 mg pseudoephedrine hydrochloride caplet to healthy volunteers with a mean peak fexofenadine plasma concentration 233 ng/mL, which occurred2.1 hours postdose. Pseudoephedrine hydrochloride, in the same study, produced a mean peak pseudoephedrine plasma concentration of 405 ng/mL which occurred 4.8 hours postdose. Co-administration of Fexofenadine HCl /pseudoephedrine HCl tablet with a high fat meal decreased fexofenadine bioavailability; however, the rate or extent of pseudoephedrine absorption was not affected. Fexofenadine HCl /pseudoephedrine HCl tablet should be taken on an empty stomach. Fexofenadine hydrochloride is rapidly absorbed following oral administration. The single and multiple dose pharmacokinetics of fexofenadine hydrochloride were linear from 20 mg to 120 mg doses. Tmax occurs at approximately 2.6 hours and Cmax is approximately 209 ng/mL following oral administration of a single 60 mg dose. Following a single 60 mg oral dose, 80% of the total fexofenadine HCl dose was recovered in the feces and 11% was recovered in the urine. Following multiple dosing, fexofenadine has an apparent elimination half-life of 11 to 16 hours. Steady state pharmacokinetic parameters following 60 mg bid dosing are: AUCss (0-12h) = 1367 ng/mL□h, Cmax = 299 ng/mL, Cmin = 29 ng/mL, tmax = 1 h. The pharmacokinetics of fexofenadine HCl in seasonal allergic rhinitis patients are similar to that of otherwise healthy subjects. Peak fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult patients.

Distribution:

Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and α1-acid glycoprotein. Pseudoephedrine hydrochloride is extensively distributed into extravascular sites (apparent volume of distribution between 2.6 and 3.5 L/kg). The protein binding of pseudoephedrine in humans is not known.

Metabolism:

Approximately 5% of the total dose of fexofenadine hydrochloride and less than 1% of the total oral dose of pseudoephedrine hydrochloride were eliminated by hepatic metabolism.

Excretion:

Pseudoephedrine HCl has been shown to have a mean elimination half-life of 4-8 hours which is dependent on urine pH. The elimination half-life is decreased at urine pH lower than 6 and may be increased at urine pH higher than 8. About 43% to 96% of an administered dose is excreted unchanged in the urine; the remainder is apparently metabolized in the liver.

Special Populations and Conditions

There are no data available on special populations following the administration of Fexofenadine HCl /pseudoephedrine HCl tablet. The following presentation is related to the pharmacokinetics in special populations following a single 80 mg oral dose of fexofenadine HCl. The pharmacokinetics were compared to those from normal subjects in a separate study of similar design. While subjects' weights were relatively uniform between the studies, the special population patients were older than the healthy, young volunteers. Thus, an age effect may be confounding the pharmacokinetic differences observed.

Pediatrics: (65 years old, n = 20) were different from those observed in healthy younger individuals following a single oral dose of 80 mg fexofenadine HCl. Mean AUC was 63% higher (control value = 1788 ng/mL□h), oral clearance 30% lower (control value = 48 L/h), renal clearance 24% less (control value = 3.6 L/h), Cmax 68% higher (control value = 248.7 ng/mL) and half-life 10% longer (15.2 h).

Gender: The steady state AUC and Cmax values in female subjects (n=20) were 33% and 46% higher, respectively, than those observed in male subjects (n=20). Renal clearance was equivalent. There was no indication of any difference in safety or efficacy.

Hepatic Insufficiency: The pharmacokinetics of fexofenadine in 14 patients with hepatic disease (moderate, n = 9; moderate to severe, n = 5), did not differ substantially from that observed in healthy subjects. The lack of effect may be explained by the fact that none of the patients investigated suffered from complete biliary obstruction, as biliary excretion is one of the major elimination pathways for fexofenadine.

Renal Insufficiency: Following a single 80 mg oral dose, renal clearance is decreased to 68, 15 and 3% of the control value (3.63 L/h) in patients with mild to moderate impairment (creatinine clearance 41-80 mL/min; n = 9), moderate to severe impairment (creatinine clearance 11-40 mL/min; n = 10) and dialysis patients (creatinine clearance.

PRECLINICAL SAFETY DATA

There are no animal or *in vitro* studies on the combination product fexofenadine hydrochloride and pseudoephedrine hydrochloride to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (area-under-the plasma concentration versus time curve [AUC]). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses up to 150 mg/kg of terfenadine for 18 and 24 months, respectively. In both species, 150 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 3 times the human AUC at the maximum recommended human daily oral dose of Fexofenadine HCl /pseudoephedrine HCl tablet.

Two-year feeding studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at doses up to 10 and 27 mg/kg, respectively (less than the maximum recommended human daily oral dose of pseudoephedrine hydrochloride on a mg/m2 basis).

In *in vitro* (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

Reproduction and fertility studies with terfenadine in rats produced no effect on male or female fertility at oral doses up to 300 mg/kg/day. However, reduced implants and post implantation losses were reported at 300 mg/kg. A reduction in implants was also observed at an oral dose of 150 mg/kg/day. Oral doses of 150 and 300 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 4 times the AUC at the maximum recommended human daily oral dose of Fexofenadine HCl /pseudoephedrine HCl tablet. In mice, fexofenadine produced no effect on male or female fertility at average dietary doses up to 4438 mg/kg (approximately 15 times the maximum recommended human daily oral dose of Fexofenadine HCl /pseudoephedrine HCl tablet based on comparison of the AUCs).

IDENTIFICATION

Xadine Plus is a purple color film coated tablet.

PRESENTATION

Xadine Plus Tablets are available in one strip of 10 tablets in each packet.

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.
- Protect from sunlight, moisture and heat.
- Store below 30°C.
- Keep all medicines out of the reach of children.

REGISTRATION NUMBER

Xadine Plus No.: 039230

Manufacturing License No.: 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mfg. U.S.P. Specs.

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan.

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