XADINE
(Fexofenadine HCl U.S.P.)

60mg, 120mg & 180mg

Tablets

COMPOSITION

Each film-coated tablet contains:
Fexofenadine hydrochloride U.S.P. 60mg
Each film-coated tablet contains:
Fexofenadine hydrochloride U.S.P. 120mg
Each film-coated tablet contains:
Fexofenadine hydrochloride U.S.P. 180mg

THERAPEUTIC INDICATIONS

Seasonal Allergic Rhinitis
Fexofenadine is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

Chronic Idiopathic Urticaria
Fexofenadine is indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. It significantly reduces pruritus and the number of wheals.

DOSAGE AND ADMINISTRATION

Seasonal Allergic Rhinitis

Adults and Children 12 Years and Older.

The recommended dose of Fexofenadine tablets is 60 mg twice daily or 120mg & 180 mg once daily with water. A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function

Chronic Idiopathic Urticaria

Adults and Children 12 Years and Older.

The recommended dose of Fexofenadine is 60 mg twice daily. A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function.

CONTRAINDICATIONS

Fexofenadine tablets, are contraindicated in patients with known hypersensitivity to fexofenadine and any of the ingredients of Fexofenadine. Rare cases of hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with most new medicinal products there is only limited data in the elderly and renally or hepatically impaired patients.

Fexofenadine hydrochloride should only be administered in these special groups on the advice of a doctor.

Patients with a history of or ongoing cardiovascular disease should be warned that, antihistamines as a medicine class, have been associated with the adverse reactions, tachycardia and palpitations and should use fexofenadine hydrochloride only on the advice of their doctor.

DRUG INTERACTIONS

Fexofenadine does not undergo hepatic biotransformation and therefore will not interact with other medicinal products through hepatic mechanisms. Coadministration of fexofenadine hydrochloride with erythromycin or ketoconazole has been found to result in a 2-3 times increase in the level of fexofenadine in plasma. The changes were not accompanied by any effects on the QT interval and were not associated with any increase in adverse reactions compared to the medicinal products given singly.

Animal studies have shown that the increase in plasma levels of fexofenadine observed after coadministration of erythromycin or ketoconazole, appears to be due to an increase in gastrointestinal absorption and either a decrease in biliary excretion or gastrointestinal secretion, respectively.

No interaction between fexofenadine and omeprazole was observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gels 15 minutes prior to fexofenadine hydrochloride caused a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave 2 hours between administration of fexofenadine hydrochloride and aluminium and magnesium hydroxide containing antacids.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no adequate data from the use of fexofenadine hydrochloride in pregnant women.

Limited animal studies do not indicate direct or indirect harmful effects with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development. Fexofenadine hydrochloride should not be used during pregnancy unless on the advice of a doctor.

Breast-feeding

There are no data on the content of human milk after administering fexofenadine hydrochloride. However, when terfenadine was administered to nursing mothers fexofenadine was found to cross into human breast milk. Therefore, fexofenadine hydrochloride is not recommended for mothers breast-feeding their babies. Breast-feeding women should only use fexofenadine hydrochloride if advised to do so by a doctor.

Fertility

No human data on the effect of fexofenadine hydrochloride on fertility are available. In mice, there was no effect on fertility with fexofenadine hydrochloride treatment.

ADVERSE DRUG REACTIONS

The following frequency rating has been used, when applicable

Very common ≥1/10;

Common ≥1/100 to <1/10;

Uncommon ≥1/1,000 to <1/100;

Rare ≥1/10,000 to <1/1,000;

Very rare <1/10,000;

Not known (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

In adults, the following undesirable effects have been reported in clinical trials, with an incidence similar to that observed with placebo

Nervous system disorders

Common: headache, drowsiness, dizziness

Gastrointestinal disorders

Common: nausea

General disorders and administration site conditions

Uncommon: fatigue

In adults, the following undesirable effects have been reported in post-marketing surveillance. The frequency with which they occur is not known (can not be estimated from available data)

Immune system disorders

Hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis

Psychiatric disorders

Insomnia, nervousness, sleep disorders or nightmares/excessive dreaming (paroniria)

Cardiac disorders

Tachycardia, palpitations

Gastrointestinal disorders

Diarrhoea

Skin and subcutaneous tissue disorders

Rash, urticaria, pruritus

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

Dizziness, drowsiness, fatigue and dry mouth have been reported with overdose of fexofenadine hydrochloride. Single doses up to 800 mg, and doses up to 690 mg twice daily for 1 month, or 240 mg once daily for 1 year have been administered to healthy subjects without the development of clinically significant adverse reactions as compared with placebo. The maximum tolerated dose of fexofenadine hydrochloride has not been established.

Standard measures should be considered to remove any unabsorbed medicinal product. Symptomatic and supportive treatment is recommended. Hemodialysis does not effectively remove fexofenadine hydrochloride from blood.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use, ATC code: R06A X26.

Mechanism of action

Fexofenadine hydrochloride is a non-sedating H_1 antihistamine. Fexofenadine is a pharmacologically active metabolite of terfenadine.

Clinical efficacy and safety

Human histamine wheal and flare studies following single and twice daily doses of fexofenadine hydrochloride demonstrate that the medicinal products exhibits an antihistaminic effect beginning within one hour, achieving maximum at 6 hours and lasting 24 hours. There is no evidence of tolerance to these effects after 28 days of dosing. A positive dose-response relationship between doses of 10 mg to 130 mg taken orally was found to exist. In this model of antihistaminic activity, it was found that doses of at least 130 mg were required to achieve a consistent effect that was maintained over a 24 hour period. Maximum inhibition in skin wheal and flare areas was greater than 80%.

No significant differences in QT_c, intervals were observed in seasonal allergic rhinitis patients given fexofenadine hydrochloride up to 240 mg twice daily for 2 weeks when compared to placebo. Also, no significant change in QT_c intervals was observed in healthy subjects given fexofenadine hydrochloride up to 60 mg twice daily for 6 months. 400 mg twice daily for 6.5 days and 240 mg once daily for 1 year, when compared to placebo.

Fexofenadine at concentrations 32 times greater than the therapeutic concentration in man had no effect on the delayed rectifier K^+ channel cloned from human heart.

Fexofenadine hydrochloride (5-10 mg/kg per orally) inhibited antigen induced bronchospasm in sensitised guinea pigs and inhibited histamine release at supra- therapeutic concentrations (10- 100 µM) from peritoneal mast cells.

Pharmacokinetic properties

Absorption

Fexofenadine hydrochloride is rapidly absorbed into the body following oral administration, with T_{max} occurring at approximately 1-3 hours post dose. The mean C_{max} value was approximately 494 ng/ml following the administration of a 180 mg dose once daily.

Distribution

Fexofenadine is 60-70% plasma protein bound.

Biotransformation and elimination

Fexofenadine undergoes negligible metabolism (hepatic or non-hepatic), as it was the only major compound identified in urine and feces of animals and man. The plasma concentration profiles of fexofenadine follow a bi-exponential decline with a terminal elimination half-life ranging from 11 to 15 hours after multiple dosing. The single and multiple dose pharmacokinetics of fexofenadine are linear for oral doses up to 120 mg BID. A dose of 240 mg BID produced slightly greater than proportional increase (8.8%) in steady state area under the curve, indicating that fexofenadine pharmacokinetics are practically linear at these doses between 40 mg and 240 mg taken daily. The major route of elimination is believed to be via biliary excretion while up to 10% of ingested dose is excreted unchanged through the urine.

PRECLINICAL SAFETY DATA

Dogs tolerated 450 mg/kg administered twice daily for 6 months and showed no toxicity other than occasional emesis. Also, in single dose dog and rodent studies, no treatment-related gross findings were observed following necropsy.

Radiolabeled fexofenadine hydrochloride in tissue distribution studies of the rat indicated that fexofenadine did not cross the blood brain barrier.

Fexofenadine hydrochloride was found to be non-mutagenic in various *in vitro* and *in vivo* mutagenicity tests.

The carcinogenic potential of fexofenadine hydrochloride was assessed using terfenadine studies with supporting pharmacokinetic studies showing fexofenadine hydrochloride exposure (via plasma AUC values). No evidence of carcinogenicity was observed in rats and mice given terfenadine (up to 150 mg/kg/day).

In a reproductive toxicity study in mice, fexofenadine hydrochloride did not impair fertility, was not teratogenic and did not impair pre- or postnatal development.

PRESENTATION

Xadine 60mg Tablets: Are available in a blister pack of 20's.

Xadine 120mg Tablets: Are available in a blister pack of 20's.

Xadine 180mg Tablets: Are available in a blister pack of 20's.

INSTRUCTIONS

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

REGISTRATION NUMBER

Xadine 60mg tablets: 034045

Xadine 120mg tablets: 034046

Xadine 180mg tablets: 034047

Manufacturing Licence 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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