FEXOFENADINE HYDROCHLORIDE - fexofenadine hydrochloride tablet, film coated
Lake Erie Medical DBA Quality Care Products LLC

Fexofenadine HCL 180 mg

DESCRIPTION

Fexofenadine hydrochloride is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl benzeneacetic acid hydrochloride. It has the following chemical structure

The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4$•HCl.

Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

Fexofenadine hydrochloride is formulated as a tablet for oral administration. Each tablet contains 30, 60, or 180 mg fexofenadine hydrochloride (depending on the dosage strength) and the following excipients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The aqueous tablet film coating is made from hypromellose, iron oxide blends, polyethylene glycol, povidone, silicone dioxide, and titanium dioxide.

CLINICAL PHARMACOLOGYMechanism of Action

Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. Both enantiomers of fexofenadine hydrochloride displayed approximately equipotent antihistaminic effects. Fexofenadine hydrochloride inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. The clinical significance of these findings is unknown. In laboratory animals, no anticholinergic or $alpha_1$-adrenergic blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

INDICATIONS AND USAGESeasonal Allergic Rhinitis

Fexofenadine Hydrochloride Tablets are 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 Hydrochloride Tablets are 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.

CONTRAINDICATIONS

Fexofenadine Hydrochloride Tablets are contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS

Information for Patients

Patients taking Fexofenadine Hydrochloride Tablets should receive the following information:

Fexofenadine Hydrochloride Tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis or for the relief of symptoms of chronic idiopathic urticaria (hives). Patients should be instructed to take Fexofenadine Hydrochloride Tablets only as prescribed. Do not exceed the recommended dose. If any untoward effects occur while taking Fexofenadine Hydrochloride Tablets, discontinue use and consult the doctor.

The product should not be used by patients who are hypersensitive to it or to any of its ingredients.

Patients should be told that this product should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant.

Patients should be advised to take the tablet with water. Patients should also be advised to store the medication in a tightly closed container in a cool, dry place, away from children.

Drug Interaction with Erythromycin and Ketoconazole

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, co-administration of fexofenadine hydrochloride with either ketoconazole or erythromycin led to increased plasma concentrations of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of either erythromycin or ketoconazole. In 2 separate studies, fexofenadine hydrochloride 120 mg twice daily (240 mg total daily dose) was co-administered with either erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to healthy volunteers (n=24, each study). No differences in adverse events or QT_c interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with either erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on steady-state fexofenadine pharmacokinetics after 7 days of co-administration with fexofenadine hydrochloride 120 mg every 12 hours (two times the recommended twice daily dose) in healthy volunteers (n=24)

Concomitant Drug	C_{maxSS} *(Peak plasma concentration)*	$AUC_{ss(0–12h)}$ *(Extent of systemic exposure)*
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro*, *in situ*, and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Drug Interactions with Antacids

Administration of 120 mg of fexofenadine hydrochloride (2 × 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox®) decreased fexofenadine AUC by 41% and Cmax by 43%. Fexofenadine hydrochloride should not be taken closely in time with aluminum and magnesium

containing antacids.

Interactions with Fruit Juices

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine hydrochloride was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the same effects may be extrapolated to other fruit juices such as apple juice. The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that Fexofenadine hydrochloride should be taken with water (see Dosage and Administration).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine hydrochloride exposure (based on plasma area-under-the-concentration vs. time [AUC] values). No evidence of carcinogenicity was observed in an 18-month study in mice and in a 24-month study in rats at oral doses up to 150 mg/kg of terfenadine (which led to fexofenadine exposures that were approximately 3 and 5 times the exposure from the maximum recommended human daily oral dose of fexofenadine hydrochloride in adults [180 mg] and children [60 mg] respectively .

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.

In rat dietary fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at an oral dose of 150 mg/kg of terfenadine (which led to fexofenadine hydrochloride exposures that were approximately 3 times the exposure of the maximum recommended human daily oral dose of 180 mg fexofenadine hydrochloride). In mice, fexofenadine hydrochloride produced no effect on male or female fertility at average dietary doses up to 4438 mg/kg (approximately 10 times the maximum recommended human daily oral dose of fexofenadine hydrochloride 180 mg based on comparison of AUCs).

PREGNANCY

Teratogenic Effects

Category C.

There was no evidence of teratogenicity in rats or rabbits at oral doses of terfenadine up to 300 mg/kg (which led to fexofenadine exposures that were approximately 3 and 30 times, respectively, the exposure from the maximum recommended human daily oral dose of fexofenadine hydrochloride of 180 mg based on comparison of AUCs).

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 hydrochloride 180 mg based on comparison of AUCs).

There are no adequate and well controlled studies in pregnant women. Fexofenadine 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 (approximately 3 times the maximum recommended human daily oral dose of fexofenadine hydrochloride of 180 mg in adults based on comparison of fexofenadine hydrochloride AUCs).

NURSING MOTHERS

It is not known if fexofenadine is excreted in human milk. There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

PEDIATRIC USE

The recommended dose in patients 6 to 11 years of age is based on cross-study comparison of the pharmacokinetics of fexofenadine hydrochloride in adults and pediatric subjects and on the safety profile of fexofenadine hydrochloride in both adult and pediatric subjects at doses equal to or higher than the recommended doses.

The safety of fexofenadine hydrochloride tablets at a dose of 30 mg twice daily has been demonstrated in 438 pediatric subjects 6 to 11 years of age in two placebo-controlled 2-week seasonal allergic rhinitis trials. The safety of fexofenadine hydrochloride for the treatment of chronic idiopathic urticaria in subjects 6 to 11 years of age is based on cross-study comparison of the pharmacokinetics of fexofenadine hydrochloride in adult and pediatric subjects and on the safety profile of fexofenadine in both adult and pediatric subjects at doses equal to or higher than the recommended dose.

The effectiveness of fexofenadine hydrochloride for the treatment of seasonal allergic rhinitis in subjects 6 to 11 years of age was demonstrated in 1 trial (n=411) in which fexofenadine hydrochloride tablets 30 mg twice daily significantly reduced total symptom scores compared to placebo, along with extrapolation of demonstrated efficacy in subjects aged 12 years and above, and the pharmacokinetic comparisons in adults and children. The effectiveness of fexofenadine hydrochloride for the treatment of chronic idiopathic urticaria in patients 6 to 11 years of age is based on an extrapolation of the demonstrated efficacy of fexofenadine hydrochloride in adults with this condition and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar in children to that of adult patients.

Three clinical safety studies comparing 15 mg twice daily (n=85) and 30 mg twice daily (n=330) of an experimental formulation of fexofenadine to placebo (n=430) have been conducted in pediatric subjects aged 6 months to 5 years. In general, fexofenadine hydrochloride was well tolerated in these studies. No unexpected adverse events were seen given the known safety profile of fexofenadine and likely adverse reactions for this patient population. (See ADVERSE REACTIONS and CLINICAL PHARMACOLOGY.)

The safety and effectiveness of fexofenadine hydrochloride in pediatric patients under 6 years of age have not been established.

GERIATRIC USE

Clinical studies of fexofenadine hydrochloride tablets and capsules did not include sufficient numbers of subjects aged 65 years and over to determine whether this population responds differently from younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger subjects. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Seasonal Allergic Rhinitis

Adults

In placebo-controlled seasonal allergic rhinitis clinical trials in subjects 12 years of age and older, which included 2461 subjects receiving fexofenadine hydrochloride capsules at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride- and placebo-treated subjects. All adverse events that were reported by greater than 1% of subjects who received the recommended daily dose of fexofenadine hydrochloride (60 mg capsules twice daily), and that were more common with fexofenadine hydrochloride than placebo, are listed in Table 1.

In a placebo-controlled clinical study in the United States, which included 570 subjects aged 12 years and older receiving fexofenadine hydrochloride tablets at doses of 120 or 180 mg once daily, adverse events were similar in fexofenadine hydrochloride- and placebo-treated subjects. Table 1 also lists adverse experiences that were reported by greater than 2% of subjects treated with fexofenadine hydrochloride tablets at doses of 180 mg once daily and that were more common with fexofenadine hydrochloride than placebo.

The incidence of adverse events, including drowsiness, was not dose-related and was similar across subgroups defined by age, gender, and race.

Table 1 Adverse experiences in subjects aged 12 years and older reported in placebo-controlled seasonal allergic rhinitis clinical trials in the United States

Twice- daily dosing with fexofenadine capsules at rates of greater than 1%		
Adverse experience	Fexofenadine 60 mg Twice Daily (n=679)	Placebo Twice Daily (n=671)
Viral Infection (cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

Once daily dosing with fexofenadine hydrochloride tablets at rates of greater than 2%		
Adverse experience	*Fexofenadine 180 mg Once Daily (n=283)*	*Placebo (n=293)*
Headache	10.6%	7.5%
Upper Respiratory Tract Infection	3.2%	3.1%

Back Pain	2.8%	1.4%

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine hydrochloride- and placebo-treated subjects.

Pediatrics

Table 2 lists adverse experiences in subjects aged 6 to 11 years of age which were reported by greater than 2% of subjects treated with fexofenadine hydrochloride tablets at a dose of 30 mg twice daily in placebo-controlled seasonal allergic rhinitis studies in the United States and Canada that were more common with fexofenadine hydrochloride than placebo.

Table 2 Adverse experiences reported in placebo-controlled seasonal allergic rhinitis studies in pediatric subjects aged 6 to 11 in the United States and Canada at rates of greater than 2%

Adverse experience	*Fexofenadine 30 mg Twice Daily (n=209)*	*Placebo (n=229)*
Headache	7.2%	6.6%
Accidental Injury	2.9%	1.3%
Coughing	3.8%	1.3%
Fever	2.4%	0.9%
Pain	2.4%	0.4%
Otitis Media	2.4%	0.0%
Upper Respiratory Tract Infection	4.3%	1.7%

Three clinical safety studies in 845 children aged 6 months to 5 years comparing 15 mg twice daily (n=85) and 30 mg twice daily (n=330) of an experimental formulation of fexofenadine to placebo (n=430) have been conducted. In general, fexofenadine hydrochloride was well tolerated in these studies. No unexpected adverse events were seen given the known safety profile of fexofenadine and likely adverse reactions for this patient population. (See PRECAUTIONS Pediatric Use.)

Chronic Idiopathic Urticaria

Adverse events reported by subjects 12 years of age and older in placebo-controlled chronic idiopathic urticaria studies were similar to those reported in placebo-controlled seasonal allergic rhinitis studies. In placebo-controlled chronic idiopathic urticaria clinical trials, which included 726 subjects 12 years of age and older receiving fexofenadine hydrochloride tablets at doses of 20 to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride- and placebo-treated patients. Table 3 lists adverse experiences in subjects aged 12 years and older which were reported by greater than 2% of subjects treated with fexofenadine hydrochloride 60 mg tablets twice daily in controlled clinical studies in the United States and Canada and that were more common with fexofenadine hydrochloride than placebo.

In a placebo-controlled clinical study in the United States, which included 167 subjects aged 12 years and older receiving fexofenadine hydrochloride 180 mg tablets, adverse events were similar in fexofenadine hydrochloride- and placebo-treated subjects. Table 3 also lists adverse experiences that were reported by greater than 2% of subjects treated with fexofenadine hydrochloride tablets at doses of 180 mg once daily and that were more common with fexofenadine hydrochloride than placebo.

The safety of fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria in pediatric patients 6 to 11 years of age is based on the safety profile of fexofenadine hydrochloride in adults and adolescent patients at doses equal to or higher than the recommended dose (see Pediatric Use).

Table 3 Adverse experiences reported in subjects 12 years of age and older in placebo-controlled chronic idiopathic urticaria studies

Twice-daily dosing with fexofenadine hydrochloride in studies in the United States and Canada at rates of greater than 2%		
Adverse experience	Fexofenadine 60 mg Twice Daily (n=191)	Placebo (n=183)
Dyspepsia	4.7%	4.4%
Myalgia	2.6%	2.2%
Back Pain	2.1%	1.1%
Dizziness	2.1%	1.1%
Pain in extremity	2.1%	0.0%
Once-daily dosing with fexofenadine hydrochloride in a study in the United States at rates of greater than 2%		
Adverse experience	*Fexofenadine 180 mg Once Daily (n=167)*	*Placebo (n=92)*
Headache	4.8%	3.3%
Nasopharyngitis	2.4%	2.2%
Upper respiratory tract infection	2.4%	2.2%

Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria subjects with 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.

OVERDOSAGE

Reports of fexofenadine hydrochloride overdose have been infrequent and contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses of fexofenadine hydrochloride up to 800 mg (6 healthy volunteers at this dose level), and doses up to 690 mg twice daily for 1 month (3 healthy volunteers at this dose level) or 240 mg once daily for 1 year (234 healthy volunteers at this dose level) were administered without the development of clinically significant adverse events as compared to placebo.

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended. Following administration of terfenadine, hemodialysis did not effectively remove fexofenadine, the major active metabolite of terfenadine, from blood (up to 1.7% removed).

No deaths occurred at oral doses of fexofenadine hydrochloride up to 5000 mg/kg in mice (110 times the maximum recommended human daily oral dose in adults and 200 times the maximum recommended human daily oral dose in children based on mg/m^2) and up to 5000 mg/kg in rats (230 times the maximum

recommended human daily oral dose in adults and 400 times the maximum recommended human daily oral dose in children based on mg/m^2). Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (300 times the maximum recommended human daily oral dose in adults and 530 times the maximum recommended human daily oral dose in children based on mg/m^2).

DOSAGE AND ADMINISTRATION

Seasonal Allergic Rhinitis

Adults and Children 12 Years and Older

The recommended dose of Fexofenadine Hydrochloride Tablets is 60 mg twice daily, or 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 (see CLINICAL PHARMACOLOGY).

Children 6 to 11 Years

The recommended dose of Fexofenadine Hydrochloride Tablets is 30 mg twice daily with water. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function (see CLINICAL PHARMACOLOGY).

Chronic Idiopathic Urticaria

Adults and Children 12 Years and Older

The recommended dose of Fexofenadine Hydrochloride Tablets is 60 mg twice daily or 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 (see CLINICAL PHARMACOLOGY).

Children 6 to 11 Years

The recommended dose of Fexofenadine Hydrochloride Tablets is 30 mg twice daily with water. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

Fexofenadine Hydrochloride Tablets 30 mg are available in HDPE bottles of 100 (NDC 66993-106-02) with a polypropylene screw cap containing a pulp/wax liner with heat-sealed foil inner seal.

Fexofenadine Hydrochloride Tablets 60 mg are available in HDPE bottles of 100 (NDC 66993-107-02) with a polypropylene screw cap containing a pulp/wax liner with heat-sealed foil inner seal and HDPE bottles of 500 (NDC 66993-104-04) with a polypropylene screw cap containing a pulp/wax liner with heat-sealed foil inner seal.

Fexofenadine Hydrochloride Tablets 180 mg are available in HDPE bottles of 100 (NDC 66993-109-02) with a polypropylene screw cap containing a pulp/wax liner with heat-sealed foil inner seal and HDPE bottles of 500 (NDC 66993-109-04) with a polypropylene screw cap containing a pulp/wax liner with heat-sealed foil inner seal.

Fexofenadine Hydrochloride Tablets are coated with a peach colored film coating. Tablets have the following unique identifiers: 30 mg tablets have 03 on one side, 60 mg tablets have 06 on one side, and 180 mg tablets have 018 on one side.

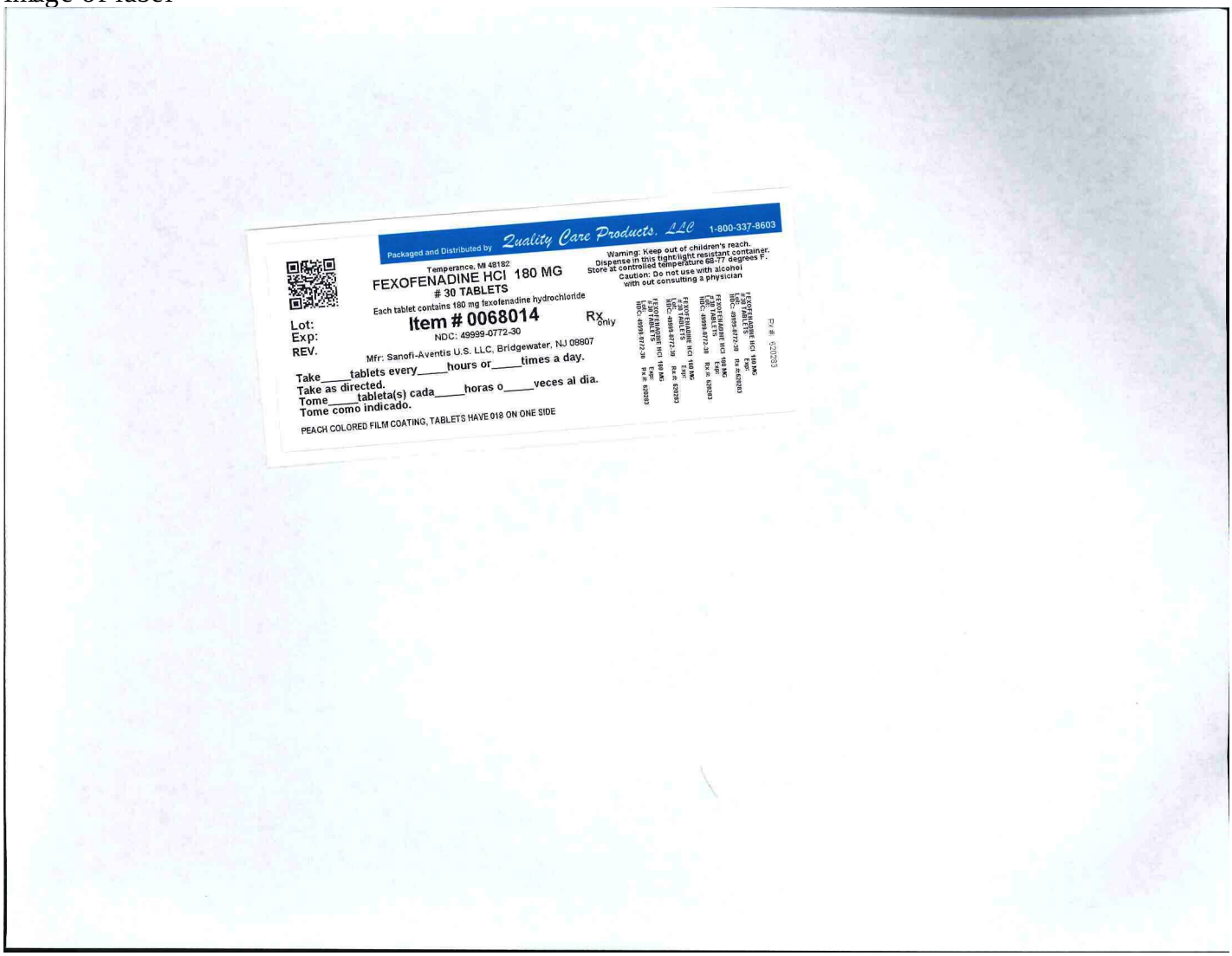
Store Fexofenadine Hydrochloride Tablets at controlled room temperature 20–25°C (68–77°F). (See USP Controlled Room Temperature). Fexofenadine Hydrochloride Tablets should be protected from

excessive moisture.

Rev. August 2006
Manufactured by:
sanofi-aventis U.S. LLC.
Bridgewater, NJ 08807 USA

Manufactured for:
Prasco Laboratories
Cincinnati, OH 45249 USA

Image of label



FEXOFENADINE HYDROCHLORIDE

fexofenadine hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49999-772(NDC:66993-109)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FEXOFENADINE HYDROCHLORIDE (UNII: 2S068B75ZU) (FEXOFENADINE - UNII:E6582LOH6V)	FEXOFENADINE HYDROCHLORIDE	180 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics			
Color	orange (peach)	**Score**	no score
Shape	OVAL (oval)	**Size**	17mm
Flavor		**Imprint Code**	018
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:49999-772-30	30 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA020872	06/07/2010	

Labeler - Lake Erie Medical DBA Quality Care Products LLC (831276758)

Establishment

Name	Address	ID/FEI	Business Operations
Sanofi-Aventis U.S. LLC		783243835	repack

Revised: 6/2010 Lake Erie Medical DBA Quality Care Products LLC