CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-447

***Name*:** Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg

***Sponsor*:** TEVA Pharmaceuticals, USA

***Approval Date*:** September 1, 2005

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APPLICATION NUMBER:

ANDA 76-447

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-447

APPROVAL LETTER

ANDA 76-447

SEP 1 2005

TEVA Pharmaceuticals, USA
Attention: Philip Erickson
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 28, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg and 180 mg.

Reference is also made to the tentative approval letter issued by this office on July 19, 2005, and to your amendment dated August 31, 2005, requesting final approval for this ANDA.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Fexofenadine Hydrochloride Tablets 30 mg, 60 mg, and 180 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Allegra Tablets 30 mg, 60 mg, and 180 mg, respectively, of Aventis Pharmaceuticals, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The listed drug product (RLD) referenced in your application, Allegra Tablets, 30 mg, 60 mg and 180 mg, of Aventis Pharmaceuticals, Inc., is subject to periods of patent protection. The following patents with their expiration dates (with pediatric extention) are currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book":

U.S. Patent Number	Expiration Date
5,578,610 (the '610 patent)	May 26, 2014
5,855,912 (the '912 patent)	August 28, 2015
5,932,247 (the '247 patent)	August 28, 2015
6,037,353 (the '353 patent)	September 14, 2017
6,113,942 (the '942 patent)	August 28, 2015
6,187,791 (the '791 patent)	November 11, 2012
6,399,632 (the '632 patent)	November 11, 2012

Your ANDA contains paragraph IV patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that each of the listed patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg and 180 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless action was brought against TEVA Pharmaceuticals, USA (TEVA) for infringement of one or more of the patents that were the subjects of paragraph IV certifications. This action must have been brought against TEVA prior to the expiration of 45 days from the date the notice you provided under Section 505 (j)(2)(B) was received by the NDA/patent holder. You have notified the agency that TEVA complied with the requirements of Section 505(j)(2)(B) of the Act, and that patent infringement litigation was brought against TEVA in the United States District Court for the District of New Jersey involving your challenge of the '912, '353, '942, '632, and '791, patents [Aventis Pharmaceuticals Inc., Merrell Pharmaceuticals Inc., and Carderm Capital L.P. v TEVA Pharmaceuticals USA, Inc., Civil Action No. 03CV487]. With respect to this ongoing patent litigation, the agency recognizes that the 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your ANDA, expired on August 11, 2005.

Furthermore, the Act provides that approval of an ANDA that contains a paragraph IV certification, and that provides for approval of the same drug product as that for which another ANDA containing a paragraph IV certification was previously received, shall be made effective not earlier than one hundred and eighty (180) days after:

1. the date the Secretary receives notice from the applicant of the previous application that commercial marketing of the drug product approved in that application was initiated, or

2. the date of a decision of a court holding the patents which were the subjects of the paragraph IV certifications to be invalid or not infringed; whichever option occurs first [section 505(j)(5)(B)(iv)].

With respect to Fexofenadine Hydrochloride Tablets 30 mg, 60 mg, and 180 mg, the Office of Generic Drugs (OGD) received and filed one or more ANDAs containing paragraph IV certifications to the listed patents prior to the filing of your ANDA. Accordingly, your application would have been eligible for final approval beginning one hundred and eighty (180) days after the first commercial marketing of the drug by one of these applicants. We refer you to the agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

However, we are able to grant final approval to your application based upon your letter dated August 31, 2005, and information submitted in conjunction with that correspondence, indicating that Barr Laboratories, Inc. (Barr) commercially launched its Fexofenadine Hydrochloride Tablets 30 mg, 60 mg, and 180 mg, under its approved ANDA on August 31, 2005. This launch served to trigger the 180-day generic drug exclusivity for this drug product. In addition, the agency was informed that Barr selectively waived the 180-day generic drug exclusivity to which Barr is entitled to TEVA Pharmaceuticals, USA. Thus, with the receipt of this waiver, the agency is permitted to grant final approval to your application for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend that you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and
Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 8/31/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-447
Division File
Field Copy
HFD-610/R. West
HFD-205

9/1/2005

Endorsements: (as provided on 7/19/05 T/A letter)
HFD-623/R.Powers/5/10/05
HFD-623/R.Bykadi/5/10/05
HFD-617/S.Eng5/10/05
HFD-613/J.Barlow/5/10/05 via eMail
HFD-613/J.Grace/5/10/05 via eMail

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APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-447

TENTATIVE APPROVAL LETTER

ANDA 76-447

JUL 19 2005

TEVA Pharmaceuticals, USA
Attention: Philip Erickson
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

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Reference is also made to your amendments dated January 5, February 3, February 22, March 22, April 26, and June 7, 2005. We also acknowledge the receipt of your correspondence dated October 15, and November 26, 2002; and February 14, and April 1, 2003, addressing patent and exclusivity issues associated with this drug product.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time due to the patent issues noted below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, Allegra Tablets, 30 mg, 60 mg and 180 mg, of Aventis Pharmaceuticals, Inc., is subject to periods of patent

protection. The following patents with their expiration dates (with pediatric extention) are currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book":

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Your ANDA contains paragraph IV patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that each of the listed patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg and 180 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless action was brought against TEVA Pharmaceuticals, USA (TEVA) for infringement of one or more of the patents that were the subjects of paragraph IV certifications. This action must have been brought against TEVA prior to the expiration of 45 days from the date the notice you provided under Section 505 (j)(2)(B) was received by the NDA/patent holder. You have notified the agency that TEVA complied with the requirements of Section 505(j)(2)(B) of the Act, and that patent infringement litigation was brought against TEVA in the United States District Court for the District of New Jersey involving your challenge of the '912, '353, '942, '632, and '791, patents [Aventis Pharmaceuticals Inc., Merrell Pharmaceuticals Inc., and Carderm Capital L.P. v TEVA Pharmaceuticals USA, Inc., Civil Action No. 03CV487].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in Section 505(j)(5)(B)(iii)[1] or such shorter or longer period as the court may have ordered, or,

[1] Because information on the '610,'912,'247,'353,'942,'791,'632, patent(s) was submitted before August 18, 2003 this reference is to a section of the Act as in effect prior to December 8, 2003 when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101©(3).

b. the date of court decides[2] that the patent(s) is/are invalid or not infringed. See Sections 505(j)(5)(B)(iii) (I), (II), and (III)], of the Act, or,

c. the listed patents have expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

Because the agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. Your amendment must provide:

1. A copy of a final order or judgment from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt.

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

In addition to, or instead of, the amendment(s) referred to above, the agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above. Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

This drug product may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under Section 501 of the Act. Also, until the agency issues the final approval letter, this drug product will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting additional amendments, please contact Simon Eng, PharmD, Project Manager, at 301-827-5848.

Sincerely yours,

Robert Lumpkin for 1/19/2005

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-447
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff
HFD-600/C. Parise
HFD-604/D. Hare

Endorsements:
HFD-623/R.Powers/ for 5/10/05
HFD-623/R.Bykadi/ S. Bykadi May 10, 2005
HFD-617/S.Eng/ 5/10/05
HFD-613/J.Barlow/
HFD-613/J.Grace/ > all John's email

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F/T by SE

Robert Lee Lost
7/19/2005

TENTATIVE APPROVAL

PS 7/7/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-447

LABELING

FEXOFENADINE HYDROCHLORIDE TABLETS

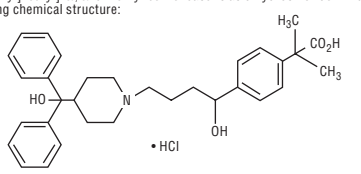
℞ only

7251
7252
7253

Iss. 1/2005

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:



$C_{32}H_{39}NO_4$•HCl M.W. 538.13

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: colloidal silicon dioxide, croscarmellose sodium, hypromellose, iron oxide black, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fexofenadine hydrochloride is an antihistamine with selective peripheral H_1-receptor antagonist activity. Both enantiomers of fexofenadine hydrochloride displayed approximately equipotent antihistaminic effects. Fexofenadine inhibited histamine release from peritoneal mast cells in rats. In laboratory animals, no anticholinergic, alpha$_1$-adrenergic or beta-adrenergic-receptor blocking effects were observed. 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.

Pharmacokinetics

Absorption

Fexofenadine hydrochloride was rapidly absorbed following oral administration of a single dose of two 60 mg capsules to healthy male volunteers with a mean time to maximum plasma concentration occurring at 2.6 hours post-dose. After administration of a single 60 mg capsule to healthy subjects, the mean maximum plasma concentration was 131 ng/mL. Following single dose oral administrations of either the 60 or 180 mg tablet to healthy, adult male volunteers, mean maximum plasma concentrations were 142 and 494 ng/mL, respectively. The tablet formulations are bioequivalent to the capsule when administered at equal doses. Fexofenadine hydrochloride pharmacokinetics are linear for oral doses up to a total daily dose of 240 mg (120 mg twice daily).

Distribution

Fexofenadine hydrochloride is 60% to 70% bound to plasma proteins, primarily albumin and α_1-acid glycoprotein.

Elimination

The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg, twice daily, in normal volunteers.

Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents unabsorbed drug or the result of biliary excretion.

Metabolism

Approximately 5% of the total oral dose was metabolized.

Special Populations

Special population pharmacokinetics (for geriatric subjects, renal and hepatic impairment), obtained after a single dose of 80 mg fexofenadine hydrochloride, were compared to those for normal subjects from a separate study of similar design. While subject weights were relatively uniform between studies, these adult special population patients were substantially older than the healthy, young volunteers. Thus, an age effect may be confounding the pharmacokinetic differences observed in some of the special populations.

Seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU) patients

The pharmacokinetics of fexofenadine hydrochloride in seasonal allergic rhinitis and chronic idiopathic urticaria patients were similar to those in healthy subjects.

Geriatric subjects

In older subjects (≥ 65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in normal volunteers (< 65 years old). Mean elimination half-lives were similar to those observed in normal volunteers.

Pediatric patients

Cross study comparisons indicated that fexofenadine hydrochloride area under the curve (AUC) following oral administration of a 60 mg dose to 7 to 12 year old pediatric allergic rhinitis patients was 56% greater compared to healthy adult subjects given the same dose. Plasma exposure in pediatric patients given 30 mg fexofenadine hydrochloride is comparable to adults given 60 mg.

Renal impairment

In patients with mild to moderate (creatinine clearance 41 to 80 mL/min) and severe (creatinine clearance 11 to 40 mL/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in normal volunteers. Peak plasma levels in patients on dialysis (creatinine clearance ≤ 10 mL/min) were 82% greater and half-life was 31% longer than observed in normal volunteers. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function (see **DOSAGE AND ADMINISTRATION**).

Hepatic impairment

The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy patients.

Effect of gender

Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine hydrochloride.

Pharmacodynamics

Wheal and Flare

Human histamine skin wheal and flare studies following single and twice daily doses of 20 and 40 mg fexofenadine hydrochloride demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2 to 3 hours, and an effect is still seen at 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing.

Histamine skin wheal and flare studies in 7 to 12 year old patients showed that following a single dose of 30 or 60 mg, antihistamine effect was observed at 1 hour and reached a maximum by 3 hours. Greater than 49% inhibition of wheal area, and 74% inhibition of flare area were maintained for 8 hours following the 30 and 60 mg dose.

Effects on QT_c

In dogs (30 mg/kg/orally twice a day), and in rabbits (10 mg/kg, infused intravenously over 1 hour) fexofenadine hydrochloride did not prolong QT_c. In dogs, the plasma fexofenadine concentration was approximately 9 times the therapeutic plasma concentrations in adults receiving the maximum recommended daily oral dose. In rabbits, the plasma fexofenadine concentration was approximately 20 times the therapeutic plasma concentration in adults receiving the maximum recommended daily oral dose. No effect was observed on calcium channel current, delayed potassium channel current, or action potential duration in guinea pig myocytes, sodium current in rat neonatal myocytes, or on several delayed rectifier potassium channels cloned from human heart at concentrations up to 1 x 10^{-5} M of fexofenadine hydrochloride.

No statistically significant increase in mean QT_c interval compared to placebo was observed in 714 seasonal allergic rhinitis patients given fexofenadine hydrochloride capsules in doses of 60 to 240 mg twice daily for two weeks. Pediatric patients from two placebo controlled trials (n = 855) treated with up to 60 mg fexofenadine hydrochloride twice daily demonstrated no significant treatment or dose-related increases in QT_c. In addition, no statistically significant increase in mean QT_c interval compared to placebo was observed in 40 healthy volunteers given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days, or in 231 healthy volunteers given fexofenadine hydrochloride 240 mg once daily for 1 year.

Clinical Studies

Seasonal Allergic Rhinitis

Adults

In three, 2 week, multicenter, randomized, double-blind, placebo-controlled trials in patients 12 to 68 years of age with seasonal allergic rhinitis (n = 1634), fexofenadine hydrochloride 60 mg twice daily significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo. Statistically significant reductions in symptom scores were observed following the first 60 mg dose, with the effect maintained throughout the 12 hour interval. In these studies, there was no additional reduction in total symptom scores with higher doses of fexofenadine hydrochloride up to 240 mg twice daily.

In one 2 week, multicenter, randomized, double-blind clinical trial in patients 12 to 65 years of age with seasonal allergic rhinitis (n = 863), fexofenadine hydrochloride 180 mg once daily significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo. Although the number of patients in some of the subgroups was small, there were no significant differences in the effect of fexofenadine hydrochloride across subgroups of patients defined by gender, age, and race. Onset of action for reduction in total symptom scores, excluding nasal congestion, was observed at 60 minutes compared to placebo following a single 60 mg fexofenadine hydrochloride dose administered to patients with seasonal allergic rhinitis who were exposed to ragweed pollen in an environmental exposure unit. In one clinical trial conducted with fexofenadine hydrochloride 60 mg capsules, and in one clinical trial conducted with fexofenadine hydrochloride and pseudoephedrine hydrochloride extended release tablets, onset of action was seen within 1 to 3 hours.

Pediatrics

Two 2 week multicenter, randomized, placebo-controlled, double-blind trials in 877 pediatric patients 6 to 11 years of age with seasonal allergic rhinitis were conducted at doses of 15, 30, and 60 mg twice daily. In one of these two studies, conducted in 411 pediatric patients, all three doses of fexofenadine hydrochloride significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo, however a dose response relationship was not seen. The 60 mg twice daily dose did not provide any additional benefit over the 30 mg twice daily dose. Furthermore, exposure in pediatric patients given 30 mg fexofenadine hydrochloride is comparable to adults given 60 mg (see **CLINICAL PHARMACOLOGY**).

Additional clinical study information related to safety of fexofenadine in pediatric patients is approved for Aventis Pharmaceuticals' fexofenadine hydrochloride drug products. However, due to Aventis Pharmaceuticals' marketing exclusivity rights, this drug product is not labeled for use in children less than 6 years of age.

Chronic Idiopathic Urticaria

Two 4 week multicenter, randomized, double-blind, placebo-controlled clinical trials compared four different doses of fexofenadine hydrochloride tablet (20, 60, 120, and 240 mg twice daily) to placebo in patients aged 12 to 70 years with chronic idiopathic urticaria (n = 726). Efficacy was demonstrated by a significant reduction in mean pruritus scores (MPS), mean number of wheals (MNW), and mean total symptom scores (MTSS, the sum of the MPS and MNW score). Although all four doses were significantly superior to placebo, symptom reduction was greater and efficacy was maintained over the entire 4 week treatment period with fexofenadine hydrochloride doses of ≥ 60 mg twice daily. However, no additional benefit of the 120 or 240 mg fexofenadine hydrochloride twice daily dose was seen over the 60 mg twice daily dose in reducing symptom scores. There were no significant differences in the effect of fexofenadine hydrochloride across subgroups of patients defined by gender, age, weight, and race.

INDICATIONS AND USAGE

Seasonal 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

Drug Interactions with Erythromycin and Ketoconazole

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

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

Concomitant Drug	C_{maxSS} *(Peak plasma concentration)*	$AUC_{SS(0\text{-}12h)}$ *(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 coadministration enhances fexofenadine gastrointestinal absorption. *In vivo* animal studies also suggest that in addition to increasing absorption, ketoconazole decreases fexofenadine hydrochloride gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Drug Interactions with Antacids

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

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 respectively approximately 3 and 5 times the exposure from the maximum recommended daily oral dose of fexofenadine hydrochloride in adults and children).

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 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 daily oral dose of fexofenadine hydrochloride in adults).

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 4 and 31 times, respectively, the exposure from the maximum recommended daily oral dose of fexofenadine in adults).

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 daily oral dose of fexofenadine hydrochloride in adults based on comparison of fexofenadine hydrochloride AUCs).

Nursing Mothers

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

The effectiveness of fexofenadine hydrochloride for the treatment of seasonal allergic rhinitis in patients 6 to 11 years of age was demonstrated in one 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 patients ages 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.

Additional clinical study information related to safety of fexofenadine in pediatric patients is approved for Aventis Pharmaceuticals' fexofenadine hydrochloride drug products. However, due to Aventis Pharmaceuticals' marketing exclusivity rights, this drug product is not labeled for use in children less than 6 years of age.

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 patients. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients. 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 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 patients 12 years of age and older, which included 2461 patients receiving fexofenadine hydrochloride capsules at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. All adverse events that were reported by greater than 1% of patients

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 patients 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 patients. **Table 1** also lists adverse experiences that were reported by greater than 2% of patients 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 patients ages 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 patients.

Pediatric
Table 2 lists adverse experiences in patients aged 6 to 11 years of age which were reported by greater than 2% of patients 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 patients ages 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%

Additional clinical study information related to safety of fexofenadine in pediatric patients is approved for Aventis Pharmaceuticals' fexofenadine hydrochloride drug products. However, due to Aventis Pharmaceuticals' marketing exclusivity rights, this drug product is not labeled for use in children less than 6 years of age.

Chronic Idiopathic Urticaria
Adverse events reported by patients 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 patients 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 patients aged 12 years and older which were reported by greater than 2% of patients 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. 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 patients 12 years and older in placebo-controlled chronic idiopathic urticaria studies in the United States and Canada at rates of greater than 2%

Adverse experience	*Fexofenadine 60 mg twice daily (n = 186)*	*Placebo (n = 178)*
Back Pain	2.2%	1.1%
Sinusitis	2.2%	1.1%
Dizziness	2.2%	0.6%
Drowsiness	2.2%	0.0%

Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients 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 (six normal volunteers at this dose level), and doses up to 690 mg twice daily for 1 month (three normal volunteers at this dose level) or 240 mg once daily for 1 year (234 normal 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.

Hemodialysis did not effectively remove fexofenadine hydrochloride from blood (1.7% removed) following terfenadine administration.

No deaths occurred at oral doses of fexofenadine hydrochloride up to 5000 mg/kg in mice (110 times the maximum recommended daily oral dose in adults and 200 times the maximum recommended daily oral dose in children based on mg/m^2) and up to 5000 mg/kg in rats (230 times the maximum recommended daily oral dose in adults and 400 times the maximum recommended 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 daily oral dose in adults and 530 times the maximum recommended 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. 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. 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. 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. 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 are available as follows:
30 mg – peach, capsule-shaped, film-coated tablets debossed with "93" on one side and "7251" on the other side, in bottles of 100 and 1000.

60 mg – peach, round, film-coated tablets debossed with "93" on one side and "7252" on the other side, in bottles of 100 and 1000.

180 mg – peach, round, film-coated tablets debossed with "93" on one side and "7253" on the other side, in bottles of 100 and 1000.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from excessive moisture.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 1/2005

NDC 0093-7251-01

FEXOFENADINE HYDROCHLORIDE
Tablets
30 mg

Each tablet contains:
fexofenadine hydrochloride 30 mg

℞ only

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from excessive moisture.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Important: This package is not child-resistant.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 12/2004

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
323K00000000

0093-7251-01

N 3 9

APPROVED
SEP - 1 2005

NDC 0093-7253-01

FEXOFENADINE HYDROCHLORIDE
Tablets
180 mg

Each tablet contains:
fexofenadine hydrochloride 180 mg

℞ only

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from excessive moisture.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Important: This package is not child resistant.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 12/2004

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0093-7253-01

N 3 3

APPROVED
SEP - 1 2005

NDC 0093-7252-01
FEXOFENADINE HYDROCHLORIDE
Tablets
60 mg
Each tablet contains: fexofenadine hydrochloride 60 mg
℞ only
100 TABLETS
TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from excessive moisture.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Important: This package is not child resistant.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss.12/2004 322K000000

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Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

0093-7252-01

NDC 0093-7252-10

FEXOFENADINE HYDROCHLORIDE
Tablets
60 mg

Each tablet contains:
fexofenadine hydrochloride 60 mg

℞ only

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from excessive moisture.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Important: This package is not child resistant.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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323K00000000

0093-7252-10

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APPROVED
SEP - 1 2005

NDC 0093-7251-10

FEXOFENADINE HYDROCHLORIDE
Tablets
30 mg

Each tablet contains:
fexofenadine hydrochloride 30 mg

℞ only

1000 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from excessive moisture.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Important: This package is not child resistant.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 12/2004

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Sellersville, PA 18960
323K00000000

0093-7251-10

N 3 1

APPROVED
SEP - 1 2005

NDC 0093-7253-10

FEXOFENADINE HYDROCHLORIDE
Tablets
180 mg

Each tablet contains:
fexofenadine hydrochloride 180 mg

℞ only

1000 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from excessive moisture.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Important: This package is not child resistant.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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0093-7253-10

N 3 5

APPROVED
SEP - 1 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-447

LABELING REVIEW

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-447

Dates of Submission: February 3, 2005; January 5, 2005; July 8, 2004; and June 28, 2002

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg

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APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes. (e-submission and paper submission)

1. CONTAINER Labels (Bottles of 100 and 1000):
   Satisfactory in final print as of the January 5, 2005 paper submission. [Vol. A4.1, Iss. 12/2004]

2. PROFESSIONAL PACKAGE INSERT:
   Satisfactory in final print as of the February 3, 2005 e-submission.
   Network path location: \\Cdsesubogd1\n76447\N_000\2005-02-03\Iss 1-2005.pdf

Revisions needed post-approval: None.

Patent Data – NDA 20-872

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5578610	Nov 26, 2013	U-139	Treatment of allergic reactions	Paragraph IV	None
5578610*PED	May 26, 2014	U-139	Treatment of allergic reactions	Paragraph IV	None
5855912	Feb 28, 2015			Paragraph IV	None
5855912*PED	Aug 28, 2015			Paragraph IV	None
5932247	Feb 28, 2015			Paragraph IV	None
5932247*PED	Aug 28, 2015			Paragraph IV	None
6037353	Mar 14, 2017	U-138	Treatment of allergic rhinitis	Paragraph IV	None
6037353*PED	Sep 14, 2017	U-138	Treatment of allergic rhinitis	Paragraph IV	None
6113942	Feb 28, 2015			Paragraph IV	None
6113942*PED	Aug 28, 2015			Paragraph IV	None
6187791	May 11, 2012	U-138	Treatment of allergic rhinitis	Paragraph IV	None
6187791*PED	Nov 11, 2012	U-138	Treatment of allergic rhinitis	Paragraph IV	None
6399632	May 11, 2012	U-468	Method of using fexofenadine HCl in treating allergic rhinitis	Paragraph IV	None
6399632*PED	Nov 11, 2012	U-468	Method of using fexofenadine HCl in treating allergic rhinitis	Paragraph IV	None

Exclusivity Data– NDA 20-872

Code	Reference	Expiration	Labeling Impact
M-25	Additional safety & PK information in children 6 months to less than 6 years of age added to package insert	May 12, 2006	Carve-out
PED	Pediatric exclusivity	Nov 12, 2006	Carve-out

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Allegra® Tablets

NDA Number: 20-872

NDA Drug Name: Allegra® (fexofenadine hydrochloride) Tablets

NDA Firm: Aventis Pharmaceuticals, Inc.

Date of Approval of NDA Insert and supplement: NDA 20-872/SE8-011; approved May 12, 2003

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Allegra® Capsules and Tablets by Aventis Pharmaceuticals, Inc. (NDA 20-872/SE8-011, approved May 12, 2003). Aventis Pharmaceuticals was granted 3 years of Hatch/Waxman exclusivity and an additional six months of pediatric exclusivity, for additional safety & pharmacokinetic information in children 6 months to less than 6 years of age that was added to the Allegra® package insert.

OGD consulted with the Office of Counter-Terrorism and Pediatric Drug Development, the Division of Pulmonary and Allergy Drug Products, and the Office of Chief Counsel to determine if the generic firms could carve out information from the pediatric studies, without compromising safety or effectiveness for the remainder of the non-exclusivity protected uses.

After some discussion, an agreement was reached regarding the carve-outs to the generic labeling and insertions of "BPCA language" that replaced the carve-outs. A memo detailing the specifics of the carve-outs and insertions to the generic labeling, was signed by Dr. Rosemary Roberts and Dr. Badrul Chowdhury on November 9, 2004. Kim Dettelbach of OCC gave her agreement to the labeling via email correspondence dated October 7, 2004.

A labeling template was created, that incorporated all of the carve-outs and insertions, and was forwarded to the generic firms. This review was actually based on this labeling template.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-872

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5578610	Nov 26, 2013	U-139	Treatment of allergic reactions	Paragraph IV	None
5578610*PED	May 26, 2014	U-139	Treatment of allergic reactions	Paragraph IV	None
5855912	Feb 28, 2015			Paragraph IV	None
5855912*PED	Aug 28, 2015			Paragraph IV	None
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6037353	Mar 14, 2017	U-138	Treatment of allergic rhinitis	Paragraph IV	None
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6187791*PED	Nov 11, 2012	U-138	Treatment of allergic rhinitis	Paragraph IV	None

6399632	May 11, 2012	U-468	Method of using fexofenadine HCl in treating allergic rhinitis	Paragraph IV	None
6399632*PED	Nov 11, 2012	U-468	Method of using fexofenadine HCl in treating allergic rhinitis	Paragraph IV	None

Exclusivity Data– NDA 20-872

Code	Reference	Expiration	Labeling Impact
M-25	Additional safety & PK information in children 6 months to less than 6 years of age added to package insert	May 12, 2006	Carve-out
PED	Pediatric exclusivity	Nov 12, 2006	Carve-out

The firm's statements are correct. [Vol. A1.1 pg. 2 of February 14, 2003 submission.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceutical Industries, Ltd.
2 Hamarpe St.
Industrial Zone Har-Hotzvim,
P.O. Box 1142
Jerusalem
Israel 91010 [Vol. B1.2 pg. 5778]

Distributor: TEVA Pharmaceuticals USA
650 Cathill Road
Sellersville, PA 18960

4. CONTAINER/CLOSURE

30 mg:
100's: 40 cc round white HDPE bottle with 33 mm metal screw non-CRC cap.
1000's: 200 cc round white HDPE bottle with 38 mm metal screw non-CRC cap.
60 mg:
100's: 40 cc round white HDPE bottle with 33 mm metal screw non-CRC cap.
1000's: 300 cc round white HDPE bottle with 53 mm metal screw non-CRC cap.
180 mg:
100's: 150 cc round white HDPE bottle with 38 mm metal screw non-CRC cap.
1000's: 1500 cc round white HDPE bottle with 53 mm metal screw non-CRC cap.
[Vol. B1.3 pg. 6184-6186]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the components and composition statement.
[Vol. B1.2 pages 5591 and 5761]

6. PACKAGING CONFIGURATIONS

RLD: Bottles of 100 and 500 (all strengths), and Blister packs of 100 (60 mg only).
ANDA: Bottles of 100 and 1000 (all strengths).
[Vol. A1.1 pg. 83]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: Store at controlled room temperature 20°- 25°C (68°- 77°F) [see USP Controlled Room Temperature]. Protect from excessive moisture.
ANDA: Store at 20°- 25°C (68°- 77°F) [see USP Controlled Room Temperature]. Protect from excessive moisture.
[Vol. A1.1 pg. 83]

8. DISPENSING STATEMENTS COMPARISON

USP: None.
RLD: Pharmacist: Dispense in light-resistant, tight container with child-resistant closure.
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant

closure (as required).
[Vol. A1.1 pg. 83]

9. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on April 20, 2005, that the firm's bioequivalency data were acceptable.

Date of Review: 5/05/05 Dates of Submission: 2/03/05; 1/05/05; 7/08/04; and 6/28/02

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 5/6/05

Team Leader: John Grace Date:

John J. Grace 5-9-2005

cc:

ANDA: 76-447
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-447

CHEMISTRY REVIEWS

#1

ANDA 76-447

Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg and 180 mg

TEVA Pharmaceuticals USA

Roslyn F. Powers, Ph.D.
Office of Generic Drugs, Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-447

2. REVIEW #1

3. REVIEW DATE: 01-NOV-2002

4. REVIEWER: Roslyn F. Powers, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	28-June-2002
Amendment	15-Oct-2002

7. NAME & ADDRESS OF APPLICANT:

Name: TEVA Pharmaceuticals USA

Address: 1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Representative: Philip Erickson, R.Ph.

Telephone: (215) 591-3000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Fexofenadine Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION:

The basis for the TEVA Pharmaceuticals USA (TEVA) proposed ANDA for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, 180 mg is the approved, reference listed drug Allegra®, the subject of application NDA #20-872 held by Aventis. Allegra® is listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations," 22nd edition (Electronic Orange Book).

A new patent has been listed for the reference listed drug, Allegra® Tablets, in the Patent Term Extension and New Patents Docket Number *95S-0117 (October 11, 2002), indicating that it will become listed in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations.* The new patent is U.S.Patent 6,399,632, expiring on May 11, 2012.

Pursuant to 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, TEVA certifies that U.S. Patents No. 6,399,632 is invalid, unenforceable, or will not be infringed by the manufacturer, use, or sale of Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, 180 mg for which this application is being submitted. TEVA will give notice under 505(j)(2)(B)(I) and (ii) to Aventis as the holder of NDA 20-872 for Allegra® Tablets and owner of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Pursuant to 505(j)(2)(A)(vii)(III) of the Federal Food, Drug, and Cosmetic Act, as amended, TEVA certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 5,578,610 will expire on November 26, 2013, U.S.Patent No. 5,855,912, U.S.Patent No. 5,932,247, and U.S.Patent No. 6,113,942 will expire on February 28, 2015, U.S.Patent No. 6,037,353 will expire on March 14, 2017, and U.S.Patent No. 6,187,791 will expire on May 11, 2012. TEVA will not engage in the commercial of Fexofenadine Hydrochloride Tablets, 30, 60 mg, & 180 mg prior to the expiration of these patents. On November 26, 2002, TEXA revised their patent certification status for the U.S.Patents Nos. 5,855,912, 5,932,247, and 6,113,942 to Paragraph IV status.

TEVA certifies that, to the best of our knowledge and in TEVA's opinion, there is one exclusivity for the reference drug product, Allegra® (fexofenadine hydrochloride) Tablets, 30 mg, 60 mg, 180 mg. The new dosage form (NDF) exclusivity will expire 2/25/03. TEVA certifies that product will not be commercially marketed until expiration of the above referenced exclusivity.

10. PHARMACOL. CATEGORY: antihistamine

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 30 mg, 60 mg, 180 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ___ OTC

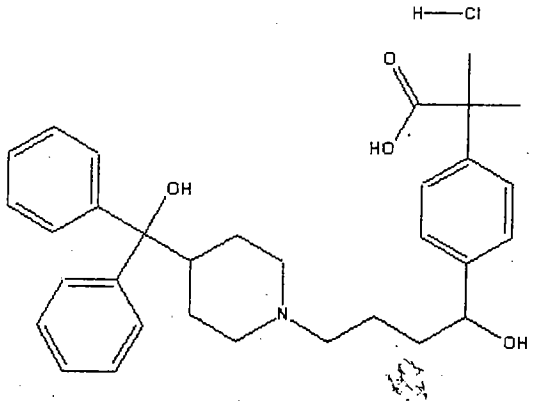
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-(alpha), (alpha)-dimethyl benzeneaetic acid. hydrochloride.
Molecular Formula: $C_{32}H_{40}ClNO_4$.
Molecular Weight: 538.1253
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Not Adequate	08-NOV-2002	RFPowers
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Withhold	12/03/02	JD'Ambrogio
Methods Validation	Pending		
Labeling	Pending		
Bioequivalence	Deficient	12/11/02	ZWahba
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-447

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not recommended for approval (MINOR Amendment).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: Fexofenadine HCl Tablets, 30 mg, 60 mg, and 180 mg, is a non-sterile product and a non-USP drug. The active agent in this immediate release dosage form is Fexofenadine Hydrochloride, a H_1-histamine receptor blocker (antihistamine). The approved, reference listed drug is Allegra®, the subject of application NDA #20-872 held by Aventis. The firm will market the product in HDPE bottles of 100 and 1000 tablets for the 30 mg, 60 mg and 180 mg strengths.

Drug Substance: Fexofenadine Hydrochloride is an off-white to white colored powder that is soluble in methanol. Fexofenadine HCl has the following chemical name/formula/MW: (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-(alpha), (alpha)-dimethyl benzeneaetic acid. hydrochloride, $C_{32}H_{40}ClNO_4$, 538.1253. Fexofenadine Hydrochloride is a non-USP drug.

Formulation and Manufacturing Process: The product formulation, in addition to Fexofenadine Hydrochloride, contains Microcrystalline Cellulose, Povidone, Lactose Monohydrate, Croscarmellose Sodium, Colloidal Silicon Dioxide, and Magnesium Stearate. [redacted]. The inactive ingredients, including those used in the [redacted], are widely used in the pharmaceutical industry and are not expected to effect the safety and effectiveness of the drug product. The formulations of the 30 mg, 60 mg, and 180 mg tablets are proportional. The product is manufactured by [redacted]

The size of the commercial batches versus the size of the ANDA batches are as follows. Production batches: [redacted]

[redacted]. The equipment and procedures used for the ANDA versus the production batches are equivalent.

Method Validation: Both Fexofenadine HCl Tablets and Fexofenadine HCl drug substance are non-USP compendial items and require method validation.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

Drug Substance:

[redacted]

Drug Product Release and Stability: [redacted]

Method Validation: [redacted]

requested.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-623/RFPowers, Ph.D./22-NOV-2002, Revised: 03-DEC-2002, 12-DEC-2002, 18-DEC-2002 RFPowers 12/20/02

HFD-623 /AMueller, Ph.D./12/18/02 AMueller 12/19/02

HFD-617 /CKiester, PM/12/18/02 CKiester 12/19/02

F/T by:ard/12/18/02

TYPE OF LETTER: NOT APPROVABLE - MINOR

C. CC Block

ANDA 76-447
ANDA DUP
DIV FILE
Field Copy

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APPEARS THIS WAY
ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #1

8.

9.

10.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available room temperature stability data for the product in the proposed packaging systems.

2. The drug substance and drug product are not compendial. Therefore, method validation is required. Once the deficiencies pertaining to this topic are satisfied, a method validation package will be sent for evaluation.

3. The Division of Bioequivalence has previously communicated deficiencies to you. Please respond with your amendment regarding these deficiencies.

4. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.

5. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

Sincerely yours,

Paul Shrout 12/19/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-447
DIV FILE
Field Copy

Endorsements

RFPowers 12/20/02

HFD-623/RFPowers, Ph.D./22-NOV-2002, Revised: 03-DEC-2002, 12-DEC-2002, 18-DEC-2002

HFD-623 /AMueller, Ph.D./12/18/02

HFD-617 /CKiester, PM/

V:\FIRMSNZ\TEVA\LTRS&REV\76447.CR1.DOC

F/T by: ard/12/18/02

TYPE OF LETTER: NOT APPROVABLE – MINOR

APPEARS THIS WAY
ON ORIGINAL

#2

ANDA 76-447

Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg and 180 mg

TEVA Pharmaceuticals, USA

Roslyn F. Powers, Ph.D.
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-447

2. REVIEW #2

3. REVIEW DATE: 01-AUG-2004

4. REVIEWER: Roslyn F. Powers, Ph.D.

5. PREVIOUS DOCUMENTS:

Original Submission	28-JUN-2002
Amendment	15-OCT-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	08-JUL-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road, PO Box 1090 North Wales, PA 19454-1090
Representative:	Philip Erickson, R.Ph.
Telephone:	(215) 591-3000
FAX:	(215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Fexofenadine Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION: The basis for the TEVA Pharmaceuticals USA (TEVA) proposed ANDA for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, 180 mg is the approved, reference listed drug Allegra®, the subject of application NDA #20-872 held by Aventis. Allegra® is listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations," 22nd edition (Electronic Orange Book).

   A new patent has been listed for the reference listed drug, Allegra® Tablets, in the Patent Term Extension and New Patents Docket Number 95S-0117 (October 11, 2002), indicating that it will become listed in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations.* The new patent is U.S.Patent 6,399,632, expiring on May 11, 2012.

   Pursuant to 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, TEVA certifies that U.S. Patent No. 6,399,632 is invalid, unenforceable, or will not be infringed by the manufacturer, use, or sale of Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, 180 mg for which this application is being submitted. TEVA will give notice under 505(j)(2)(B)(I) and (ii) to Aventis as the holder of NDA 20-872 for Allegra® Tablets and owner of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

   Pursuant to 505(j)(2)(A)(vii)(III) of the Federal Food, Drug, and Cosmetic Act, as amended, TEVA certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 5,578,610 will expire on November 26, 2013, U.S.Patent No. 5,855,912, U.S.Patent No. 5,932,247, and U.S.Patent No. 6,113,942 will expire on February 28, 2015, U.S.Patent No. 6,037,353 will expire on March 14, 2017, and U.S.Patent No. 6,187,791 will expire on May 11, 2012. TEVA will not engage in the commercial of Fexofenadine Hydrochloride Tablets, 30, 60 mg, & 180 mg prior to the expiration of these patents. On November 26, 2002, TEVA revised their patent certification status for the U.S.Patent Nos. 5,855,912, 5,932,247, and 6,113,942 to Paragraph IV status.

   TEVA certifies that, to the best of our knowledge and in TEVA's opinion, there are two exclusivities for the reference drug product, Allegra® (Fexofenadine Hydrochloride) Tablets, 30 mg, 60 mg, 180 mg. The following exclusivities are currently listed:

   M-25 for the additional safety and PK information in children 6 months to less than 6 years of age added to package insert that expires on May 12, 2006.

   PED (Pediatric Exclusivity) which expires on November 12, 2006.
   PED (Pediatric Exclusivity) which expired on August 25, 2003.

M-25 exclusivity will expire on May 12, 2006 and its extension by Pediatric Exclusivity will expire on November 12, 2006. TEVA certifies that insert labeling for the drug product proposed herein will not include information protected by these exclusivities until the expiration of PED associated with M-25 on November 12, 2006.

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 30 mg, 60 mg, 180 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ___OTC

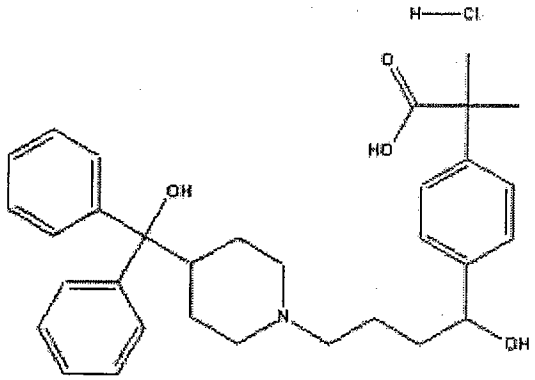
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-(alpha), (alpha)-dimethyl benzeneaetic acid. hydrochloride.
Molecular Formula: $C_{32}H_{40}ClNO_4$.
Molecular Weight: 538.1253
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	26-FEB-2004 (stamp date)	BLim-reviewer
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Acceptable	28-MAY-2003	ZWahba
EA	N/A per Policy		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-447

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

30 mg: Peach capsule shaped, film coated tablet. One side is debossed with the number "93" and the other side is debossed with the number "7251".

60 mg: Peach round, film coated tablet. One side is debossed with the number "93" and the other side is debossed with the number "7252".

180 mg: Peach round, film coated tablet. One side is debossed with the number "93" and the other side is debossed with the number "7253".

Drug Substance:

Fexofenadine Hydrochloride is an off-white to white colored powder that is soluble in methanol.

B. Description of How the Drug Product is Intended to be Used

See package insert

C. Basis for Approvability or Not-Approval Recommendation

CMC- Not Acceptable

[ ]

[redacted]

Labeling- Pending

EES- Pending an update

Bioequivalence-Acceptable

Expiration Date- 24 months substantiated through real time stability data

III. Administrative

A. Reviewer's Signature

Roslyn F. Powers 9/27/2004

B. Endorsement Block

HFD-623/RFPowers, Ph.D./02-AUG-2004; Revised: 16-AUG-2004
HFD-623 /AMueller, Ph.D./ AMueller 9-28-04

F/T by:

TYPE OF LETTER:

C. CC Block

ANDA 76-447
ANDA DUP
DIV FILE
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confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 76-447
DIV FILE
Field Copy

RFPowers 9/27/04

Endorsements
HFD-623/RFPowers, Ph.D./02-AUG-2004, Revised: 16-AUG-2004
HFD-623 /AMueller, Ph.D./8/16/04
HFD-617 /SEng, PM/9/27/04

9/28/04

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F/T by: ard/9/27/04

TYPE OF LETTER: NOT APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

#3

ANDA 76-447

Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg and 180 mg

TEVA Pharmaceuticals, USA

Roslyn F. Powers, Ph.D.
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-447

2. REVIEW #3

3. REVIEW DATE: 17-MAR-2005

4. REVIEWER: Roslyn F. Powers, Ph.D.

5. PREVIOUS DOCUMENTS:

Original Submission	28-JUN-2002
Amendment	15-OCT-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	08-JUL-2004
Minor Amendment	22-FEB-2005
Unsolicited Amendment	22-MAR-2005
Telephone Amendment	26-APR-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road, PO Box 1090 North Wales, PA 19454-1090
Representative:	Philip Erickson, R.Ph.
Telephone:	(215) 591-3000
FAX:	(215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Fexofenadine Hydrochloride Tablets

1. LEGAL BASIS FOR SUBMISSION: The basis for the TEVA Pharmaceuticals USA (TEVA) proposed ANDA for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, 180 mg is the approved, reference listed drug Allegra®, the subject of application NDA #20-872 held by Aventis Pharmaceuticals. Allegra® is listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations," 22nd edition (Electronic Orange Book).

   A new patent has been listed for the reference listed drug, Allegra® Tablets, in the Patent Term Extension and New Patents Docket Number 95S-0117 (October 11, 2002), indicating that it will become listed in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations.* The new patent is U.S.Patent 6,399,632, expiring on May 11, 2012.

   Pursuant to 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, TEVA certifies that U.S. Patent No. 6,399,632 is invalid, unenforceable, or will not be infringed by the manufacturer, use, or sale of Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, 180 mg for which this application is being submitted. TEVA will give notice under 505(j)(2)(B)(I) and (ii) to Aventis as the holder of NDA 20-872 for Allegra® Tablets and owner of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

   Pursuant to 505(j)(2)(A)(vii)(III) of the Federal Food, Drug, and Cosmetic Act, as amended, TEVA certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 5,578,610 will expire on November 26, 2013, U.S.Patent No. 5,855,912, U.S.Patent No. 5,932,247, and U.S.Patent No. 6,113,942 will expire on February 28, 2015, U.S.Patent No. 6,037,353 will expire on March 14, 2017, and U.S.Patent No. 6,187,791 will expire on May 11, 2012. TEVA will not engage in the commercial of Fexofenadine Hydrochloride Tablets, 30, 60 mg, & 180 mg prior to the expiration of these patents. On November 26, 2002, TEVA revised their patent certification status for the U.S.Patent Nos. 5,855,912, 5,932,247, and 6,113,942 to Paragraph IV status.

   TEVA certifies that, to the best of our knowledge and in TEVA's opinion, there are two exclusivities for the reference drug product, Allegra® (Fexofenadine Hydrochloride) Tablets, 30 mg, 60 mg, 180 mg. The following exclusivities are currently listed:

   M-25 for the additional safety and PK information in children 6 months to less than 6 years of age added to package insert that expires on May 12, 2006.

   PED (Pediatric Exclusivity) which expires on November 12, 2006.
   PED (Pediatric Exclusivity) which expired on August 25, 2003.

M-25 exclusivity will expire on May 12, 2006 and its extension by Pediatric Exclusivity will expire on November 12, 2006. TEVA certifies that insert labeling for the drug product proposed herein will not include information protected by these exclusivities until the expiration of PED associated with M-25 on November 12, 2006.

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 30 mg, 60 mg, 180 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ___OTC

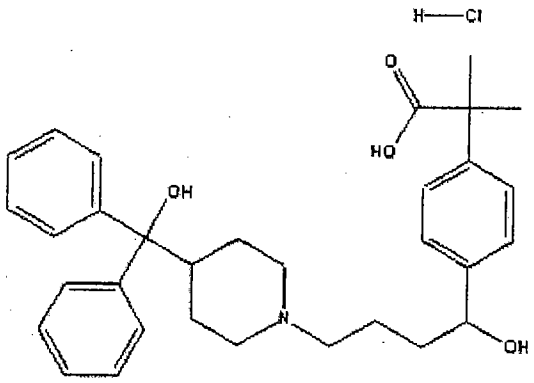
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-(alpha), (alpha)-dimethyl benzeneaetic acid. hydrochloride.
Molecular Formula: $C_{32}H_{40}ClNO_4$.
Molecular Weight: 538.1253
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	15-JUN-2005	RPowers-Reviewer
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11-APR-2005	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	9-MAY-2005	D. Catterson
Bioequivalence	Acceptable	28-MAY-2003	ZWahba
EA	N/A per Policy		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes _X___ No _____ If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-447

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

30 mg: Peach capsule shaped, film coated tablet. One side is debossed with the number "93" and the other side is debossed with the number "7251".

60 mg: Peach round, film coated tablet. One side is debossed with the number "93" and the other side is debossed with the number "7252".

180 mg: Peach round, film coated tablet. One side is debossed with the number "93" and the other side is debossed with the number "7253".

Drug Substance:

Fexofenadine Hydrochloride is off-white to white colored powder that is soluble in methanol.

B. Description of How the Drug Product is Intended to be Used

Maximum daily dose: 180 mg

C. Basis for Approvability or Not-Approval Recommendation

CMC, Bio, Labeling and EER are acceptable.

III. Administrative

A. Reviewer's Signature

Roslyn F Powers 7/6/2005

B. Endorsement Block

HFD-623/RFPowers, Ph.D./17-MAR-2005; Revised: 11-APR-2005; 13-APR-2005; 29-APR-2005; 15-JUN-2005; 06-JUL-2005
HFD-623 /D'Costa, Ph.D./ 7/8/05
HFD-617/SEng, PM/ 7/8/05

F/T by:

TYPE OF LETTER:

C. CC Block

ANDA 76-447
ANDA DUP
DIV FILE
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confidential commercial

information from

CHEMISTRY REVIEW #3

The firm has substantiated the proposed expiration date of 24 months.

D. Post Approval Commitments: Satisfactory in CR #3

The firm commits to place the first commercial batch on long-term stability and report the results in the annual reports.

30. MICROBIOLOGY: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: N/A

32. LABELING: Acceptable

33. ESTABLISHMENT INSPECTION: Acceptable

11-APR-2005	S. Adams

34. BIOEQUIVALENCE: Acceptable

28-MAY-2003	ZWahba

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: N/A per Policy

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-447

BIOEQUIVALENCE REVIEWS

Fexofenadine Hydrochloride Tablets
30 mg, 60 mg and 180 mg
ANDA 76-447
Reviewer: Z.Z. Wahba
V:\Firmsam\Teva\ltrs&revs\76447N0602.doc

Teva Pharmaceuticals USA
North Wales, PA
Submission Date: 06/28/02

Review of Two Bioequivalence Studies, Dissolution Data And Two Waiver Requests

Introduction

Indication: The drug is indicated for relief of symptoms associated with seasonal allergic rhinitis.
Type of Submission: Original ANDA
Contents of Submission: Single-dose fasting and non-fasting studies (180 mg), and dissolution data (30 mg, 60 mg and 180 mg).
RLD: Aventis Pharms' Allegra Tablets, 180 mg, 60 mg, and 30 mg.

Background

Fexofenadine hydrochloride is rapidly absorbed following oral administration with a mean time to maximum plasma concentration occurring at 2.6 hours post-dose. After administration of a single 60 mg capsule to healthy subjects, the mean maximum plasma concentration was 131 ng/mL. Following single dose oral administrations of either the 60 and 180 mg tablet to healthy, adult male volunteers, mean maximum plasma concentrations were 142 and 494 ng/mL, respectively. The tablet formulations are bioequivalent to the capsule when administered at equal doses. Fexofenadine hydrochloride pharmacokinetics are linear for oral doses up to a total daily dose of 240 mg (120 mg twice daily).

Fexofenadine hydrochloride is 60% to 70% bound to plasma proteins, primarily albumin and (alpha) $_1$ -acid glycoprotein. The mean elimination half-life of fexofenadine is approximatly 14.4 hours following administration of 60 mg, twice daily, in normal volunteers. Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents unabsorbed drug or the result of biliary excretion.

I. Single-dose Fasting Bioequivalence Study, 180 mg strength (Protocol No.: ——— R01-861)

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	———
Medical Investigator	———, M.D.
Principle Investigator:	———, Pharm. D.
Clinical Study Dates:	Period 1: Group 1: 02/23/02; Group 2: 03/09/92

	Period 2: Group 1: 03/02/02; Group 2: 03/16/02
Analytical Facility	[redacted]
Analytical Study Dates:	03/08/02 to 04/16/02

Information on pages 277, 282, 283, 469, 1816, volume C1.2 and C1.5.

TREATMENT INFORMATION

Treatment ID:	T (Test)	R (Reference)
Product Name:	Fexofenadine Tablets, 180 mg	Allegra Tablets, 180 mg
Applicant:	Teva	Aventis Pharmaceuticals
Manufacture Date:	12/04/01	N/A
Expiration Date:	N/A	08/03
Batch/Lot Number:	K-29076	1033334
ANDA Batch Size:	[redacted]units	N/A
Potency:	97.7%	99.4%
Content Uniformity:	99.4%	101.3%
Strength:	180 mg	180 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	1X180 mg	1X180 mg
Study Condition:	Fasting	Fasting

Information on pages 90, 101, 280, volumes C1.1, C1.2.

RANDOMIZATION **DESIGN**

Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	7 days

DOSING **SUBJECTS**

Single or Multiple Dose:	Single	**IRB Approval:**	Y
No. of Subjects enrolled: Group 1 = Subjects 1-48; Group 2 = Subjects 49-60	60	**No. of Subjects Completing:** (Subject # 1-60)	60
No. of Dropouts:	0	**No. of Subjects used for statistical analysis:**	60

Demographic Data	• 60 subjects enrolled. • Gender: 42 males, 18 females • Race: 57 Caucasian, 1 American Indian, 2 Asian • Age: Average 24 years (18-47 years) No subjects < 18 years 58 subjects between 18-40 years

	2 subjects between 41-64 years No subjects between 65-75 years No subjects > 75 years • Height (cm): Average 173.6 (152.4 – 190.5) • Weight (kg): Average 77.3 (53.5-102.8)
Blood Sampling:	Pre-dose and at the following times post-dose: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours. Plasma was stored at -20°C until analysis. Note: Some deviations related to blood sampling times were observed in the study. These deviations should not influence the outcome of this study.

Adverse Events:
A total of 16 post-dosing adverse events were reported (Test treatment=10, Reference treatment=6). The adverse events were judged as: 8 possibly drug related, and 8 unrelated to the drug treatment (pages 289290, 402, volume C1.2).

Assay Methodology: (NOT TO BE RELEASED UNDER FOI)

Study Sample Reassays: (see page 1821, volume C1.5)
A number of samples were repeated for the following reasons:

Reason for repeat	Number of samples	% of total samples
Spoiled sample	47	2.45%
Pharmacokinetic Anomalies	33	1.72%
Sample outside range	181	9.43%

Note: Total number of study samples is 1920.
The samples were repeated in accordance with the firm's SOP 19.3.2 revision 02.

Comment on the Analytical Method: The analytical method is acceptable.

Pharmacokinetics:

The firm conducted the study in two groups. The group effect was examined with the SAS-GLM using the following model: group seq trt per(group) sub(seq*group) group*trt group*seq. No significant group*trt effects was found for the pharmacokinetic parameters LAUCt, LAUCi and LCMAX.

The plasma concentrations and pharmacokinetic parameters of fexofenadine under fasting conditions were further analyzed using SAS-GLM procedure for analysis of variance without the "group" term in the model.

PK Results under fasting conditions:
Mean Plasma Concentrations:Table 1, Figure 1
Pharmacokinetic Parameters: Tables 2 and 3

90% Confidence Intervals:

LAUC0-t	85.01 - 98.03%
LAUC0-inf	85.22 - 97.87%
LCmax	80.25 - 96.48%

Root MSE:	LAUC0-t	0.23340202
	LAUC0-inf	0.22659760
	LCmax	0.30167627

Comments on the study under fasting conditions:

- There was no observation of a first measurable drug concentration reported as Cmax.
- There was no observation of measurable pre-dose drug concentration.
- The reviewer recalculated pharmacokinetic parameters. The firm's reported values are in agreement with those obtained by the reviewer.
- The 90% confidence intervals for log transformed AUC0-t, AUC0-inf, and Cmax are within acceptable limits of 80-125%.

I. Single-Dose Non-Fasting Bioequivalence Study, 180 mg strength (Protocol No.: R01-862)

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Investigator	[redacted] M.D.
Principle Investigator:	[redacted] Pharm. D.
Clinical Study Dates:	Period 1: 01/06/02 Period 2: 01/13/02
Analytical Facility	[redacted]
Analytical Study Dates:	01/21/02 to 02/07/02

Information on pages 4221-4235, 4815, volume C1.9, C1.11.

TREATMENT INFORMATION

Treatment ID:	T (Test)	R (Reference)
Product Name:	Fexofenadine Tablets, 180 mg	Allegra Tablets, 180 mg
Applicant:	Teva	Aventis Pharmaceuticals
Manufacture Date:	12/04/01	N/A
Expiration Date:	N/A	08/03
Batch/Lot Number:	K-29076	1033334
Strength:	180 mg	180 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	1X180 mg	1X180 mg
Study Condition:	Non-Fasting (following a standardized breakfast)	Non-Fasting (following a standardized breakfast)

Information on pages 4113-4117, volume C1.9.

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	7 days

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
No. of Subjects participated:	24	**No. of Subjects Completing:** (Subject # 1-20, and 22-24)	23
No. of Dropouts: Subject #21 was dropped by the clinical investigators prior to Period 2 dosing due to a positive pregnancy screen at check-in.	1	**No. of Subjects used for statistical analysis:**	23

Demographic Data	• 24 subjects enrolled. • Gender: 17 males, 7 females • Race: 23 Caucasian, 1 American Indian • Age: Average 26.3 years (19-53 years) No subjects < 18 years 21 subjects between 18-40 years 3 subjects between 41-64 years No subjects between 65-75 years No subjects > 75 years • Height (cm): Average 174.6 (154.9 – 170.2) • Weight (kg): Average 76.5 (53.5 – 99.2)
Blood Sampling:	Pre-dose and at the following times post-dose: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours. Plasma was stored at -20°C until analysis. Note: Some deviations related to blood sampling times were observed in the study. These deviations should not influence the outcome of this study.

Adverse Events:

A total of 8 post-dosing adverse events were reported (Test treatment=3, Reference treatment=5). The adverse events were judged as: 1 possibly drug related, 1 remotely drug related, and 6 unrelated to the drug treatment (pages 4233, 4303, volume C1.9).

Assay Methodology: (NOT TO BE RELEASED UNDER FOI)

Study Sample Reassays: (see page 4818, volume C1.11)
A number of samples were repeated for the following reasons:

Reason for repeat	Number of samples	% of total samples
Spoiled sample	2	0.22%
Sample outside range	17	1.85%

Note: Total number of study samples is 920.

Pharmacokinetics:
The plasma concentrations and pharmacokinetic parameters of fexofenadine under non-fasting conditions were analyzed using SAS-GLM procedure for analysis of variance.

PK Results:
Mean Plasma Concentrations:Table 4, Figure 2
Pharmacokinetic Parameters: Tables 5 and 6

Geometric T/R Ratios:	AUC0-t	0.88
	AUC0-inf	0.88
	Cmax	0.81

Comments on the non-fasting study:

- There was no observation of a first measurable drug concentration reported as Cmax.
- There was no one subject with measurable pre-dose drug concentration.
- The T/R geometric mean ratios for AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25.
- The reviewer recalculated pharmacokinetic parameters. The reported values are in agreement with those obtained by the firm.
- The 90% confidence intervals for log transformed AUC0-t, and AUC0-inf, are within acceptable limits of 80-125%. The 90% confidence intervals for log transformed CMAX are outside the acceptable

limits of 80-125%. However, currently, the 90% confidence intervals for log transformed AUC0-t, and AUC0-inf and CMAX are not required by DBE for non-fasting BE studies.

Formulation (Not to be released under FOI)

- Formulation information is provided in Table 7.
- All inactive ingredients in the formulation are present at levels within the range cited in the FDA Inactive Ingredient Guide (1996) for approved drug products.

Dissolution (Not to be released under FOI)

- The dissolution information is provided in Table 8.
- The firm conducted its dissolution based on its in-house dissolution testing:
  Dissolution Medium: [redacted]
  Volume: 900 mL
  Dissolution Apparatus: Apparatus 2 (Paddle)
  RPM: 50
- There is no official dissolution method for Fexofenadine HCl tablets.

Deficiency Comment:

The dissolution testing conducted by Teva on its Fexofenadine HCl tablets 180 mg, 60 mg, and 30 mg , is incomplete. The firm used its in-house method for dissolution testing. The DBE requests the firm to conduct the dissolution testing under the following conditions (per DBE database):

Apparatus:	USP Apparatus II (Paddle) at 50 rpm
Medium:	900 mL 0.001 N HCl (30 and 60 mg)
	1800 mL 0.001 N HCl (180 mg)
Sampling Times:	10, 20, 30 and 45 minutes.

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Recommendations

1. The two bioequivalence studies, one under fasting (project # ——— R01-861) and the other under non-fasting (project # ——— R01-862) conditions, conducted by Teva Pharmaceuticals on its Fexofenadine Hydrochloride Tablets, 180 mg, Lot # K-29078, comparing it to the RLD Aventis Pharms' Allegra Tablets, 180 mg, Lot # 1033334, have been found acceptable. However, the application is incomplete for the reason given in the deficiency comment.

2. The dissolution testing conducted by the firm on its Fexofenadine HCl 30 mg, 60 mg and 180 mg tablets is incomplete due to the reasons given in the deficiency comment. Therefore, the waivers of the in vivo bioequivalence studies for 30 mg and 60 mg tablets of the test product cannot be granted.

3. The firm is requested to conduct dissolution testing using the following "interim" method:

Apparatus:	USP Apparatus II (Paddle) at 50 rpm
Medium:	900 mL 0.001 N HCl (30 and 60 mg)
	1800 mL 0.001 N HCl (180 mg)
Sampling Times:	10, 20, 30 and 45 minutes.

4. The firm should be informed of the recommendations and deficiency.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED GJPSINGH
FT INITIALED GJPSINGH Date: 12-5-02

Concur: Dale P. Conner Date: 12/9/02
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Table #1
Mean Plasma Concentrations (ng/mL) of Fexofenadine Under Fasting Conditions)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	68.50	76.57	86.05	104.99	0.80
0.67	231.51	170.66	273.45	208.84	0.85
1	309.21	184.28	357.04	218.30	0.87
1.33	345.56	208.56	388.25	209.90	0.89
1.67	367.00	216.15	395.54	192.41	0.93
2	376.70	217.24	398.33	177.88	0.95
2.5	355.81	181.84	387.88	164.13	0.92
3	350.37	181.54	370.49	165.40	0.95
3.5	319.34	166.86	342.48	154.65	0.93
4	299.95	147.78	315.11	138.55	0.95
5	245.52	99.44	267.31	116.26	0.92
6	204.89	82.96	215.76	90.17	0.95
8	115.43	46.26	117.13	55.69	0.99
10	68.31	28.33	68.72	31.21	0.99
12	46.53	17.29	47.33	18.88	0.98
16	25.42	9.27	26.52	9.22	0.96
24	12.98	5.02	13.56	4.40	0.96
36	6.24	4.04	7.33	3.44	0.85
48	0.66	2.01	1.53	3.01	0.43

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R
UNITS: PLASMA LEVEL=NG/ML, TIME=HRS

FIG P–1 . PLASMA FEXOFENADINE LEVELS

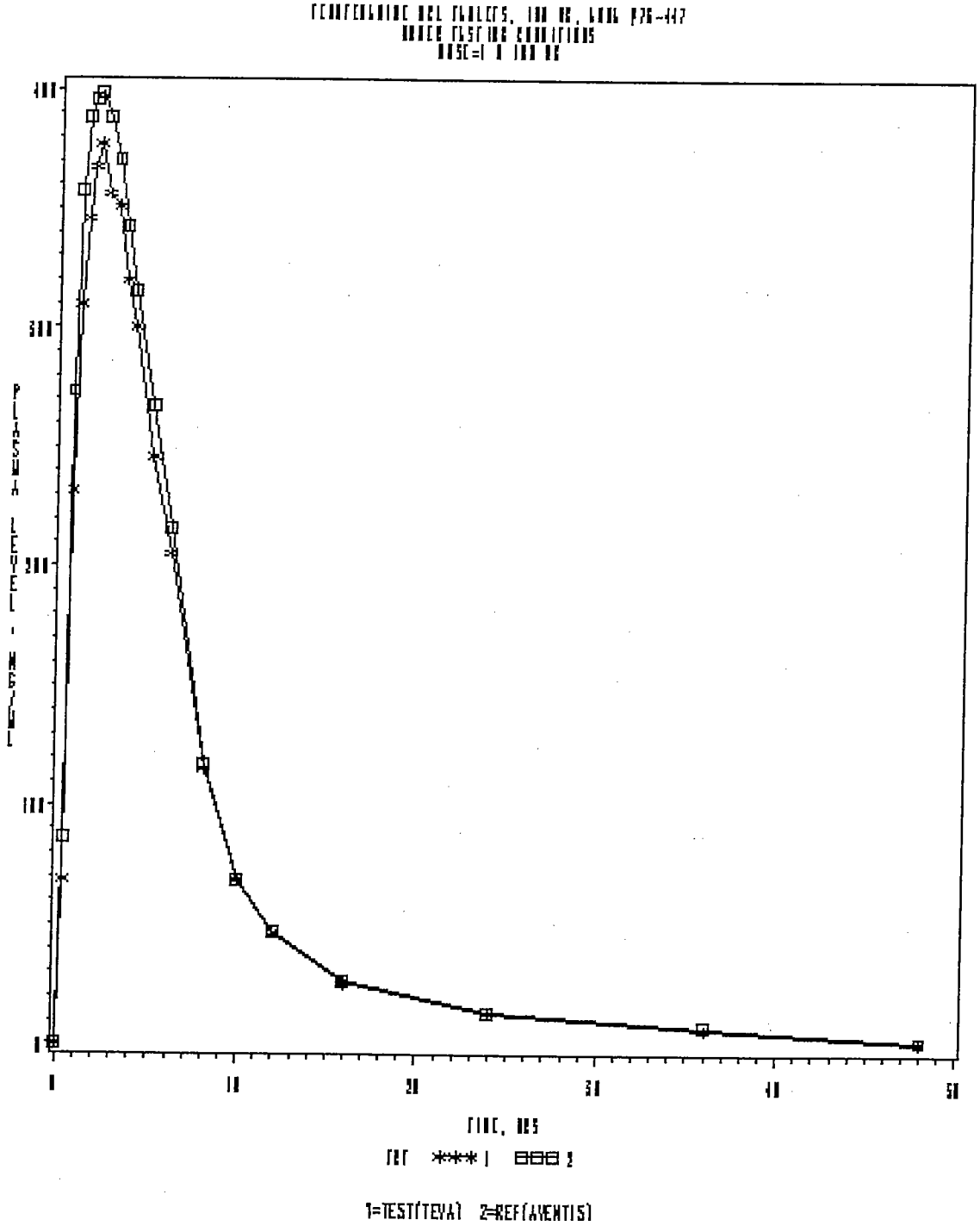

Table #2
Summary of Pharmacokinetics Parameters (Fexofenadine) Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	2814.79	1132.18	3024.53	1104.18	0.93
AUCT	2711.80	1118.20	2912.63	1092.78	0.93
CMAX	449.60	216.08	498.95	204.30	0.90
KE	0.09	0.04	0.08	0.04	1.16
LAUCI	2601.11	0.41	2850.71	0.34	0.91
LAUCT	2495.78	0.42	2736.25	0.35	0.91
LCMAX	403.95	0.47	460.10	0.41	0.88
THALF	8.96	4.09	10.42	4.61	0.86
TMAX	2.22	1.22	2.14	1.18	1.04

UNITS: AUC=NG HR/ML, CMAX=NG/ML , TMAX=HR, T/2=HR

Table #3
LSMeans and 90% Confidence Intervals (Fexofenadine)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	2604.13	2851.47	0.91	85.22	97.87
LAUCT	2498.54	2737.05	0.91	85.01	98.03
LCMAX	404.48	459.69	0.88	80.25	96.48

LSM1=LS mean test LSM2=LS mean reference
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML

Table #4
Mean Plasma Concentrations (ng/mL) of Fexofenadine Under Non-Fasting Conditions)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	5.71	10.61	4.13	10.09	1.38
0.67	54.96	83.73	42.23	70.25	1.30
1	98.56	107.10	101.31	111.70	0.97
1.33	159.80	110.98	176.35	136.34	0.91
1.67	199.29	112.94	240.45	148.76	0.83
2	242.28	120.88	272.24	145.60	0.89
2.5	244.55	94.17	280.67	123.73	0.87
3	244.64	89.36	282.26	113.69	0.87
3.5	241.37	88.26	281.56	115.40	0.86
4	226.45	92.67	266.88	105.06	0.85
5	166.22	60.52	218.47	120.82	0.76
6	136.11	51.42	165.43	82.35	0.82
8	83.86	36.14	97.29	50.43	0.86
10	54.11	25.49	58.32	27.02	0.93
12	37.71	14.74	39.49	18.20	0.95
16	22.50	8.12	24.29	9.99	0.93
24	12.19	4.67	13.20	5.35	0.92
36	6.63	4.89	6.65	5.50	1.00
48	3.04	4.17	2.89	4.15	1.05

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R
UNITS: PLASMA LEVEL=NG/ML, TIME=HRS

FIG P–1 . PLASMA FEXOFENADINE LEVELS

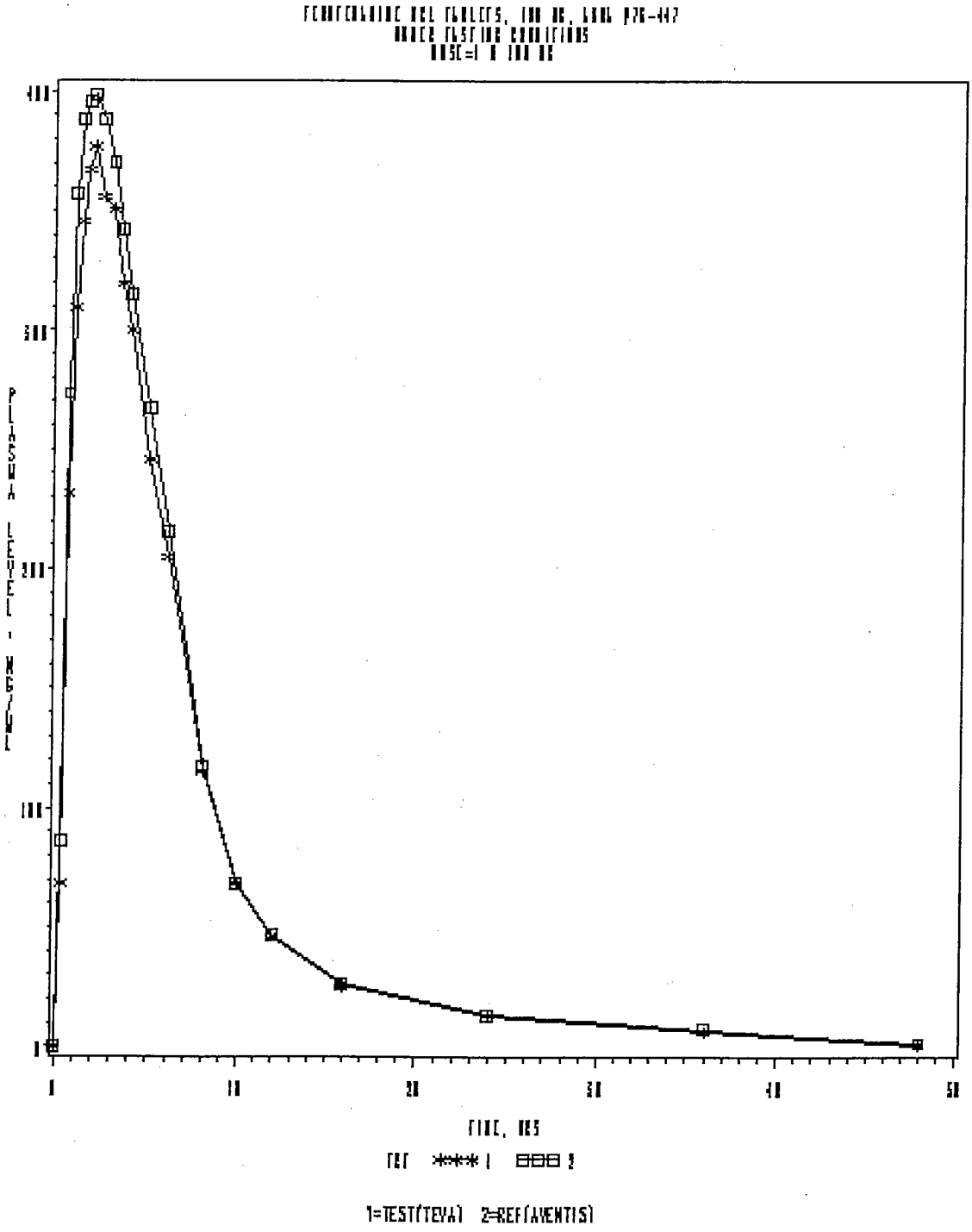

Table #5
Summary of Pharmacokinetics Parameters (Fexofenadine)
Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	2061.26	627.94	2324.97	718.31	0.89
AUCT	1894.48	562.00	2159.85	671.03	0.88
CMAX	311.45	99.83	382.48	119.07	0.81
KE	0.08	0.05	0.07	0.04	1.11
LAUCI	1954.92	0.35	2214.53	0.33	0.88
LAUCT	1803.27	0.34	2057.81	0.33	0.88
LCMAX	295.61	0.34	363.42	0.34	0.81
THALF	13.90	14.57	13.08	7.82	1.06
TMAX	2.57	1.19	2.78	1.20	0.92

UNITS: AUC=NG HR/ML, CMAX=NG/ML , TMAX=HR, T/2=HR

Table #6
LSMeans and 90% Confidence Intervals (Fexofenadine)
Under Non-Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	1964.38	2220.83	0.88	85.01	92.03
LAUCT	1813.97	2064.31	0.88	83.85	92.09
LCMAX	296.22	364.24	0.81	75.46	87.65

LSM1=LS mean test LSM2=LS mean reference
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML

TABLE #7. FORMULATION (information on page 113, 115, volume C1.1)

Ingredient	Amount (mg)/Tablet			% per tablet
	30 mg strength	60 mg strength	180 mg strength	
Fexofenadine HCl	30.0	60.0	180.0	29.13
Microcrystalline Cellulose NF				
[redacted]				
Povidone USP [redacted]				
Lactose Monohydrate NF [redacted]				
Croscarmellose Sodium NF [redacted]				
[redacted]				
Colloidal Silicon Dioxide NF [redacted]				
Magnesium Stearate NF				
[redacted] (Peach)				
[redacted]				
Total	103.0	206.0	618.0	100%
Composition of the film coating [redacted] [redacted] (Peach)				
Hydroxypropyl Methylcellulose USP [redacted]				
Titanium Dioxide USP				
Polyethylene Glycol NF				
Iron Oxide Yellow NF				
Iron Oxide Red NF				
Iron Oxide Black				
Total				

Test Product:
30 mg – peach capsule shape, film coated tablets debossed with "93" on one side and "7251" on the other side, in bottles of 100 and 1000.
60 mg – peach round. film coated tablets debossed with "93" on one side and "7251" on the other side, in bottles of 100 and 1000.
180 mg – peach round, film coated tablets debossed with "93" on one side and "7251" on the other side, in bottles of 100 and 1000.

Reference Product:
Tablets have the following unique identifiers: 30 mg tablets have 03 on one side and either 0088 or scripted E on the other, 60 mg tablets have 06 on one side and either 0088 or scripted E on the other; and 180 mg tablets have 018 on one side and either 0088 or scripted E on the other.

TABLE #8. DISSOLUTION DATA
(information on pages 104-111, volume C1.1)

The firm conducted the dissolution testing according to its in-house dissolution testing method:
No. Units Tested: 12 tablets
USP 25 apparatus: 2 (Paddle)
Medium: ——
Volume: 900 mL
RPM: 50
Test Product: Teva's Fexofenadine HCl Tablets, 30 mg, 60 mg, and 180 mg.
Reference Product: Aventis Pharms' Allegra Tablets, 30 mg, 60 mg, and 180 mg.

Sampling Times (minutes)	Test Product Strength: 30 mg Lot #K-29079			Reference Product Strength: 30 mg Lot #1031601		
	Mean %	Range	% CV	Mean %	Range	% CV
15	80		4.7	84		2.0
30	88		2.8	92		1.2
45	91		2.4	94		2.5
60	93		2.5	96		1.0
	Test Product Strength: 60 mg Lot #K-29078			Reference Product Strength: 60 mg Lot #1022724		
15	83		3.6	91		1.6
30	89		2.6	95		1.4
45	91		2.8	96		1.5
60	93		3.1	96		1.4
	Test Product Strength: 180 mg Lot #K-29076			Reference Product Strength: 180 mg Lot #1033334		
15	86		2.3	84		1.7
30	90		1.6	91		1.3
45	92		1.7	94		1.7
60	93		1.5	95		1.1

BIOEQUIVALENCY DEFICIENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:74-447 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg.

The Division of Bioequivalence has completed its review of your submission and the following deficiencies have been identified:

The Division of Bioequivalence requests that dissolution testing should be conducted under the following conditions:

Apparatus:	USP Apparatus II (Paddle) at 50 rpm
Medium:	900 mL 0.001 N HCl (30 and 60 mg)
	1800 mL 0.001 N HCl (180 mg)
Sampling Times:	10, 20, 30 and 45 minutes.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-447
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba ZW 12/04/02
HFD-658/ GJP Singh GJPS 12-5-02
HFD-650/ D. Conner DC 12/5/02

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BIOEQUIVALENCY - INCOMPLETE Submission date: 06/28/02

1. FASTING STUDY (STF) Strength: 180 mg
Outcome: AC

Clinical Study Site: [redacted]
Analytical Site: [redacted]

2. FOOD STUDY (STP) Strength: 180 mg
Outcome: AC

Clinical Study Site: [redacted]
Analytical Site: [redacted]

~~3. Dissolution (DIS) Strengths: 180 mg~~ SM
Outcome: IC

4. WAIVER (WAI) Strengths: 30 mg
Outcome: IC

5. WAIVER (WAI) Strengths: 60 mg
Outcome: IC

NOTE:
AC - Acceptable UN - Unacceptable
NC - No Action IC - Incomplete

Outcome Decision: **Incomplete**

MAY 28 2003

Fexofenadine HCl Tablets
30 mg, 60 mg, and 180 mg
ANDA #**76-447**
Reviewer: Z.Z. Wahba
V:\new\firmsnz\TEVA\ltrs&rev\76447A0303.doc

TEVA Pharmaceuticals USA
North Wales, PA
Submission Date: March 20, 2003

REVIEW OF AN AMENDMENT

BACKGROUND

- The firm previously submitted two in vivo bioequivalence studies under fasting and non-fasting conditions comparing its Fexofenadine Hydrochloride Tablets, 180 mg, to the RLD, Aventis Pharms' Allegra Tablets, 180 mg. The application also contained dissolution data and a request for waiver of in vivo bioequivalence study requirements for the 30 mg and 60 mg tablets. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review date 12/09/02) due to the following deficiency comment.

  The Division of Bioequivalence requests that dissolution testing should be conducted under the following conditions:

Apparatus:	USP Apparatus II (Paddle) at 50 rpm
Medium:	900 mL 0.001 N HCl (30 and 60 mg)
	1800 mL 0.001 N HCl (180 mg)
Sampling Times:	10, 20, 30 and 45 minutes.

- In this submission, the firm has responded to the deficiency comment and included additional information in the current submission.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT

DISSOLUTION DATA

(information in the 03/20/03 Amendment, Attachment #3, pages 10-17, volume A2.1).

Drug (Generic Name): Fexofenadine HCl Tablets, 30 mg, 60 mg & 180 mg.
Reference Drug: Aventis Pharms' Allegra® Tablets, 30 mg, 60 mg & 180 mg.

Method:	FDA Method (OGD/DBE Electronic Database)
USP Apparatus:	II (Paddle)
Medium:	0.001 N Hydrochloric Acid
Volume:	900 mL 0.001N HCL (30, 60 mg) or 1800 mL (180 mg)
RPM:	50
No. Unit Tested:	12
Assay Method:	———————————
Tolerance:	NLT — % (Q) in 10 minutes and NLT — % (Q) in 30 minutes.

Sampling Times (MINUTES)	Test Product: Fexofenadine Tablets Lot Number: K-29079 Strength: 30 mg			Reference Product: Allegra® Tablets Lot Number: 1045751 Strength: 30 mg		
	%Mean	Range	%RSD	%Mean	Range	%RSD
10	88		2.9	71		4.0
20	93		3.6	87		2.3
30	95		3.5	93		2.0
45	96		3.9	97		1.1
F_2 Comparison	N/A					

Sampling Times (MINUTES)	Test Product: Fexofenadine Tablets Lot Number: K-29078 Strength: 60 mg			Reference Product: Allegra® Tablets Lot Number: 1045620 Strength: 60 mg		
	%Mean	Range	%RSD	%Mean	Range	%RSD
10	89		3.5	91		1.5
20	95		1.9	98		1.8
30	97		1.4	100		0.9
45	98		1.3	101		1.3
F_2 Comparison	N/A					

Fexofenadine 180 mg
Comparative Dissolution Profiles (In 1800 mL)

Sampling Times (MINUTES)	Test Product: Fexofenadine Tablets Lot Number: K-29076 Strength:180 mg			Reference Product: Allegra® Tablets Lot Number: 1033334 Strength: 180 mg		
	%Mean	Range	%RSD	%Mean	Range	%RSD
10	84		4.4	75		7.6
20	90		4.0	84		6.7
30	93		3.2	87		6.3
45	95		2.5	91		4.5
F_2 Comparison	N/A					

180 mg strength was used in the *in vivo* bioequivalence studies.

Comments on the dissolution data:

- The test and reference products meet the specifications of NLT —%(Q) of the labeled amount of fexofenadine is dissolved in 10 minutes and NLT —% (Q) of the labeled amount of fexofenadine is dissolved in 30 minutes.
- The dissolution testing is acceptable.

RECOMMENDATIONS

1. The two bioequivalence studies, one under fasting (project # —— R01-861) and the other under non-fasting (project # —— R01-862) conditions, conducted by Teva Pharmaceuticals on its Fexofenadine Hydrochloride Tablets, 180 mg, Lot # K-29078, comparing it to the RLD Aventis Pharms' Allegra Tablets, 180 mg, Lot # 1033334, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting and non-fasting conditions Teva's Fexofenadine Hydrochloride Tablets, 180 mg, is bioequivalent to the RLD, Aventis Pharms' Allegra Tablets, 180 mg.

2. The dissolution testing submitted by the firm on its Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.001 N HCl for the 30 mg and 60 mg strengths and 1800 mL of 0.001 N HCl for the 180 mg strength at 37°C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

   NLT —%(Q) of the labeled amount of fexofenadine is dissolved in 10 minutes and NLT —% (Q) of the labeled amount of fexofenadine is dissolved in 30 minutes.

4. The formulations for the 30 mg and 60 mg tablets are proportionally similar to the 180 mg tablets which underwent acceptable bioequivalence testing. Waivers of *in vivo* bioequivalence study requirements for the 30 mg and 60 mg tablets of the test product are granted based on 21 CFR 320.22 (d)(2). The 30 mg and 60 mg tablets are therefore deemed bioequivalent to Aventis Pharms' Allegra Tablets, 30 mg, and 60 mg, respectively.

6. From the bioequivalence standpoint, the firm has met the in vivo bioequivalence study and in vitro dissolution testing requirements and thus, the application is acceptable.

Zakaria Z Wahba

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED GJPSINGH
FT INITIALED GJPSINGH Gurjaspal Singh Date: 5-23-03

Concur: Dale P. Conner Date: 5/28/03
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-447 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Fexofenadine HCl Tablets, 30 mg, 60 mg & 180 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

We acknowledge that dissolution testing has been incorporated into your stability and quality control programs. For the 30 mg and 60 strengths, the dissolution testing should be conducted in 900 mL 0.001 N HCl using USP Apparatus II (paddle) at 50 rpm. For the 180 mg strength, the dissolution testing should be conducted in 1800 mL 0.001 N HCl using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications: NLT —%(Q) in 10 minutes and NLT —% (Q) in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-447
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Z. Wahba
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba 5/27/03
HFD-658/ GJP Singh GJPS 5-23-03
HFD-650/ D. Conner 5/28/03

V:\new\firmsnz\TEVA\ltrs&rev\76447A0303.doc

BIOEQUIVALENCY - ACCEPTABLE

1. STUDY AMENDMENT (STA) Strengths: 30 mg, 60 mg,180 mg
Outcome: AC

Outcome Decisions: AC - ACCEPTABLE

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-447 SPONSOR : Teva Pharmaceuticals USA
DRUG AND DOSAGE FORM : Fexofenadine Hydrochloride Tablets
STRENGTH(S) : 30 mg, 60 mg, and 180 mg.
TYPES OF STUDIES : Fasting and fed studies, dissolution data.
CLINICAL STUDY SITE(S) : [redacted]
ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : The two bioequivalence studies demonstrate that under fasting and fed conditions, Teva's Fexofenadine Hydrochloride Tablets, 180 mg, are bioequivalent to the reference product, RLD Aventis Pharms' Allegra Tablets, 180 mg.

DISSOLUTION : The dissolution testing for test and reference products (30 mg, 60 mg and 180 mg) is acceptable.
WAIVER: The waiver of bioequivalence requirements for the strengths 30 mg, and 60 mg are granted.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic no New facility ___ For cause ___ other ___	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 5/27/03

TEAM LEADER : Gur-Jai Pal Singh, Ph.D. BRANCH : III

INITIAL : Gurjapal Singh DATE : 5-27-03

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 5/28/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-447

ADMINISTRATIVE DOCUMENTS

77-081, 76-502, 76-447, 76-191, ——, 76-169

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: November 9, 2004

From: Badrul A. Chowdhury, M.D., Ph.D., HFD-570 Badrul A. Chowdhury
Director
Division of Pulmonary and Allergy Drug Products

Through: Rosemary Roberts, M.D., HFD-950 Rosemary Roberts
Director
Office of Counter Terrorism and Pediatric Drug Development

To: Gary J. Buehler, R. Ph., HFD-600
Director
Office of Generic Drugs

Re: Proposed Labeling for Generic Allegra (fexofenadine hydrochloride) capsules and tablets

The Office of Generic Drugs (OGD) consulted the Division of Pulmonary and Allergy Drug Products regarding acceptable package insert labeling for generic Allegra (fexofenadine hydrochloride) capsules and tablets. OGD has asked if the generic firms could carve out information from pediatric studies, without compromising safety or effectiveness for the remainder of the non-exclusivity protected uses. This labeling, which was approved on May 12, 2003, has been granted 3 years of Hatch/Waxman exclusivity.

The approved pediatric protected additions to the Allegra labeling, and the proposed generic carve-outs were consulted to the Office of Counter Terrorism and Pediatric Drug Development and the Division of Pulmonary and Allergy Drug Products by the Office of Generic Drugs. All parties have reviewed the pertinent sections of the current Allegra package insert and commented on the impact of each proposed deletion on the safety and effectiveness of the drug product. The conclusion reached was that generic firms **could** carve-out the pediatric labeling sections without rendering generic products less safe or effective for all remaining non-protected conditions of use.

Under the approach proposed by OGD and acceptable to this division, these **bolded** sections of the package insert for generic Allegra (fexofenadine hydrochloride) capsules and tablets will have the following changes:

SECTIONS CHANGED:

CLINICAL PHARMACOLOGY:
Clinical Studies:
Seasonal Allergic Rhinitis:
Pediatrics:

Current ALLEGRA Package Insert without carve-out:

Pediatrics. Two 2-week multicenter, randomized, placebo-controlled, double-blind trials in 877 pediatric patients 6 to 11 years of age with seasonal allergic rhinitis were conducted at doses of 15, 30, and 60 mg twice daily. In one of these two studies, conducted in 411 pediatric patients, all three doses of fexofenadine hydrochloride significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo, however a dose response relationship was not seen. The 60 mg twice daily dose did not provide any additional benefit over the 30 mg twice daily dose. Furthermore, exposure in pediatric patients given 30 mg fexofenadine hydrochloride is comparable to adults given 60 mg (see CLINICAL PHARMACOLOGY).
Three clinical safety studies in 845 children aged 6 months to 5 years with allergic rhinitis comparing 15 mg BID (n=85) and 30 mg BID (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 and ADVERSE REACTIONS.)

ANDA Package Insert with carve-out:

Pediatrics. Two 2-week multicenter, randomized, placebo-controlled, double-blind trials in 877 pediatric patients 6 to 11 years of age with seasonal allergic rhinitis were conducted at doses of 15, 30, and 60 mg twice daily. In one of these two studies, conducted in 411 pediatric patients, all three doses of fexofenadine hydrochloride significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo, however a dose response relationship was not seen. The 60 mg twice daily dose did not provide any additional benefit over the 30 mg twice daily dose. Furthermore, exposure in pediatric patients given 30 mg fexofenadine hydrochloride is comparable to adults given 60 mg (see CLINICAL PHARMACOLOGY).
Additional clinical study information related to safety of fexofenadine in pediatric patients is approved for Aventis Pharmaceuticals' fexofenadine hydrochloride drug products. However, due to Aventis Pharmaceuticals' marketing exclusivity rights, this drug product is not labeled for use in children less than 6 years of age.

PRECAUTIONS:
Pediatric Use:

Current ALLEGRA Package Insert without carve-out:

Pediatric Use

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

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

The effectiveness of ALLEGRA for the treatment of seasonal allergic rhinitis in patients 6 to 11 years of age was demonstrated in one trial (n=411) in which ALLEGRA tablets 30 mg twice daily significantly reduced total symptom scores compared to placebo, along with extrapolation of demonstrated efficacy in patients ages 12 years and above, and the pharmacokinetic comparisons in adults and children. The effectiveness of ALLEGRA 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 ALLEGRA 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 BID (n=85) and 30 mg BID (n=330) of an experimental formulation of fexofenadine to placebo (n=430) have been conducted in pediatric patients 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 the age of 6 months have not been established.

ANDA Package Insert with carve-out:

Pediatric Use

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

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

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extrapolation of the demonstrated efficacy of ALLEGRA 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.
Additional clinical study information related to safety of fexofenadine in pediatric patients is approved for Aventis Pharmaceuticals' fexofenadine hydrochloride drug products. However, due to Aventis Pharmaceuticals' marketing exclusivity rights, this drug product is not labeled for use in children less than 6 years of age.

ADVERSE REACTIONS:
Seasonal Allergic Rhinitis:
Pediatric:

Current ALLEGRA Package Insert without carve-out:

Pediatric. Table 2 lists adverse experiences in patients aged 6 to 11 years of age which were reported by greater than 2% of patients 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 patients ages 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 BID (n=85) and 30 mg BID (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.)

ANDA Package Insert with carve-out:

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

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Otitis Media	2.4%	0.0%
Upper Respiratory Tract Infection	4.3%	1.7%

Additional clinical study information related to safety of fexofenadine in pediatric patients is approved for Aventis Pharmaceuticals' fexofenadine hydrochloride drug products. However, due to Aventis Pharmaceuticals' marketing exclusivity rights, this drug product is not labeled for use in children less than 6 years of age.

RECORD OF TELEPHONE CONVERSATION

FDA: [redacted] FDA: Fax us a copy of this phone amendment and follow with a hard copy to FDA please. Firm: Yes. End of the T-CON	DATE: April 20, 2005 ANDA NUMBER: 76-447 PRODUCT NAME: Fexofenadine HCl Tabs INITIATED BY: FIRM __ FDA x_ FIRM NAME: TEVA FIRM REPRESENTATIVE: Philip Erickson TELEPHONE NUMBER: 215-591-3141 FDA REPRESENTATIVE: R. Powers, Ph.D. R Powers 4/29/05 S.Eng R 4/20/05 SIGNATURE

CC: ANDA
DIVISION FILE
Chem Div I, T-con Notebook

Location: V:\FIRMSNZ\TEVA\TELECONS\76447.4.20.05.tcon.doc

RECORD OF TELEPHONE CONVERSATION

FDA: [redacted]

Firm: OK, we can do that and we will check with our supplier. After that we will revise the [redacted] to indicate this specification.

FDA: Fax us a copy and follow with a hard copy to FDA please.

Firm: Yes.

End of the T-CON

DATE: June 1, 2005

ANDA NUMBER: 76-447

PRODUCT NAME:
Fexofenadine HCl Tabs, 30, 60, and 180 mg

INITIATED BY:

FIRM __ FDA _x

FIRM NAME:

TEVA

FIRM REPRESENTATIVE:
D. Jaskot, Philip Erickson

TELEPHONE NUMBER:

215-591-3141

FDA REPRESENTATIVE:
Paul Schwartz, Ph.D. 6/17/05
Y.Amin 6/17/05
S.Eng 6/17/05

SIGNATURE

CC: ANDA
DIVISION FILE
Chem Div I, T-con Notebook

Location: V:\FIRMSNZ\TEVA\TELECONS\76447.tcon.6.1.05.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-447 Applicant TEVA Pharmaceuticals, USA

Drug Fexofenadine HCl Strength(s) Tablets 30mg 60mg, 180mg

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER: **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch

Date 2 May 2005 Initials MMS

Date 7/19/05 Initials raw for

Contains GDEA certification: Yes No
(required if sub after 6/1/92)

Determ. of Involvement? Yes No

Pediatric Exclusivity System

RLD = NDA# 20-872

Patent/Exclusivity Certification: Yes No

Date Checked 7/19/05

If Para. IV Certification- did applicant

Nothing Submitted

Notify patent holder/NDA holder Yes No

Written request issued

Was applicant sued w/in 45 days: Yes No

Study Submitted

Has case been settled: Yes No Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes No (not determined)

Date of latest Labeling Review/Approval Summary

Any filing status changes requiring addition Labeling Review Yes No

Type of Letter: PIV's to All Listed Patents - Teva was sued on 1353, 632, 741, 937, 942.

Comments: Also sued on '872 which was not listed in O.B. 30 month exp 8/11/2005

Eligible for TA only

2. Project Manager, Simon Eng Team 1
Review Support Branch

Date 5/9/05 Initials

Date Initials

Original Rec'd date 6/28/02 7/1/02

Date Acceptable for Filing

Patent Certification (type) IV III

Date Patent/Exclus.expires

Citizens' Petition/Legal Case Yes No

(If YES, attach email from PM to CP coord)

First Generic Yes No

Radika has Barr's ANDA 76169

EER Status Pending Acceptable OAI

Date of EER Status 4/11/05

Date of Office Bio Review 5/28/03

Date of Labeling Approv. Sum 5/9/05

Labeling Acceptable Email Rec'd Yes No

Labeling Acceptable Email filed Yes No

Date of Sterility Assur. App.

Methods Val. Samples Pending Yes No

MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No

Modified-release dosage form: Yes No

Suitability Petition/Pediatric Waiver

Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved Date

Previously reviewed and CGMP def. /NA Minor issued Date

Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included
OGD Regulatory Counsel, Post-MMA Language Included
Comments:

Date 5/13/05 Initials DR

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments:

Date 7/19/05 Initials

Cmt OK

OS not in effect!

REVIEWER:

FINAL ACTION

5. Frank Holcombe — **First Generics Only**
Assoc. Dir. For Chemistry
Date _____
Initials _____
Comments: (First generic drug review)
Multiple ANDAs have been approved/tentatively approved for Fexofenadine HCl and Pseudoephedrine HCl Extended-release Tablets, 60 mg/120mg and Fexofenadine HCl Capsules, 60mg.

6. Vacant
Deputy Dir., DLPS
RLD = Allegra Tablets 30mg, 60mg, 180mg. Aventis Pharmaceuticals Inc. NDA 20-872 (001, 002, 004)
Date _____
Initials _____

7. Peter Rickman
Director, DLPS
Date 7/19/05
Initials [signature] for
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: Acceptable ES dtd. 4/11/05 (Verified 7/19/05), NDAI alerts noted. Bioequivalence studies on the 180mg strength (fasting and non-fasting) found acceptable 5/23/03. Dissolution testing on all 3 strengths also found acceptable 5/23/03. Waivers granted to the 30mg and 60mg strengths under 21 CFR 320.22(d)(2). Both study test sites have acceptable OSI inspectional histories. Office level bio endorsed 5/28/03. Labeling found acceptable (FR) 5/9/05. CMC found acceptable 7/8/05. Methods validation was completed and found acceptable.

8. Robert L. West
Deputy Director, OGD
Date 7/19/2005
Initials [signature]
Para.IV Patent Cert: (Yes) No ; Pending Legal Action: (Yes) No ; Petition: Yes No
Comments: TEVA made paragraph IV certifications to each of the listed patents; e.g., '610, '912, '247, '353, '942, '791, '632 (1/8/03 submission). TEVA was sued within the 45-day period over the '912, '353, '942, '791, and '632 patents. The statutory 30-month period ends on 8/11/05. M-25 exclusivity has been satisfactorily addressed under the "carve-out". This ANDA is recommended for tentative approval.

9. Gary Buehler
Director, OGD
Date 7/19/05
Initials [signature] for
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

10. Project Manager, Team Simon Eng
Review Support Branch
Date 7-19-05
Initials [signature] for
NH Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
3:09 pm Time notified of approval by phone 3:18 Time approval letter faxed
FDA Notification:
7-19-05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7-19-05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou9.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-447 Applicant TEVA Pharmaceuticals USA
Drug FEXOFENADINE HCl Tablets Strength(s) 30mg, 60mg, 180mg

APPROVAL X TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

	DRAFT Package	FINAL Package
1. Martin Shimer, Chief, Reg. Support Branch	Date 8/26/05 Initials RWS	Date 8/26/05 Initials RWS for MF

Contains GDEA certification: (Yes) No (required if sub after 6/1/92)
Determ. of Involvement? Yes (No)
Pediatric Exclusivity System
RLD = NDA# 20-892
Patent/Exclusivity Certification: (Yes) No
Date Checked Previously granted
If Para. IV Certification- did applicant
Notify patent holder/NDA holder (Yes) No
Nothing Submitted
Was applicant sued w/in 45 days (Yes) No
Written request issued
Has case been settled: Yes (No) Date settled:
Study Submitted
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes (No)
Type of Letter:
Comments: TEVA made paragraph IV certifications to all listed patents. TEVA's 30-month stay ended 8/1/05. Barr has effectively waived its eligibility for 180-day generic drug exclusivity to TEVA. This ANDA is eligible for full approval.

2. Project Manager, Team ___ Review Support Branch Simon Eng	Date ___ Initials ___	Date ___ Initials ___

Original Rec'd date
Date Acceptable for Filing
Patent Certification (type)
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes No
(If YES, attach email from PM to CP coord)
First Generic Yes No
Acceptable Bio reviews tabbed Yes No
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted Rejected Pending

EER Status Pending Acceptable OAI
Date of EER Status
Date of Office Bio Review
Date of Labeling Approv. Sum
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes No
MV Commitment Rcd. from Firm Yes No
Modified-release dosage form: Yes No
Interim Dissol. Specs in AP Ltr: Yes

Previously reviewed and tentatively approved Date
Previously reviewed and CGMP def. /NA Minor issued Date
Comments:

3. David Read (PP IVs Only) OGD Regulatory Counsel,	Pre-MMA Language included Post-MMA Language Included	Date ___ Initials ___

Comments:

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III		Date 8/26/05 Initials RWS for MF

Comments:
Approval package was previously endorsed by Raul Schwartz on 7/7/05 prior to its tentative approval on 7/19/05. In its request for final approval, TEVA has stated that "no changes have been made to the product ... since the tentative approval

REVIEWER: FINAL ACTION

5. Frank Holcombe First Generics Only Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for Fexofenadine HCl in combination with Pseudoephedrine HCl or tentatively approved for this combination. Barr's ANDA K-169 for Fexofenadine HCl Capsules was also approved. This ANDA was tentatively approved on 7/19/05.

6. Vacant
Deputy Dir., DLPS RLD- Allegra Tablets 30mg 60mg 180mg Date_____
Initials_____
Aventis Pharmaceuticals Inc. NDA 20-872 (001, 002, 004)

7. Peter Rickman Date_____
Director, DLPS Initials_____
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: Acceptable EES dated 4/11/05 (Verified 8/26/05). No O.A.I. Claims noted. Refer to the ANDA tentative approval summary completed at the time of the TA issued on 7/19/05. In TEVA's request for approval, TEVA states "no changes have been made to this product or its labeling since the tentative approval was granted."
OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: (Yes) No ; Pending Legal Action: (Yes) No ; Petition: Yes (No)
Comments: TEVA's 30-month statutory hold expired on 8/11/05. Barr is eligible for 180-day generic drug exclusivity for this drug product with respect to all patents and strengths. However, TEVA's ANDA may be granted final approval because Barr has triggered its exclusivity and in a letter dated August 31, 2005 Barr has selectively waived the 180-day exclusivity to TEVA. Thus, this ANDA is recommended for approval. /RW.

9. Gary Buehler Date 8/31/05
Director, OGD Initials GB
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue

10. Project Manager, Team ~~Simon Eng~~ Date_____
Review Support Branch Initials _____
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
_____Time notified of approval by phone _____Time approval letter faxed
FDA Notification:
_____Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
_____Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-447

CORRESPONDENCE

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3141
FAX: (215) 591 8812

June 28, 2002

505(j)(2)(A) OK
19-AUG-2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg, and 180 mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg. Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 31 volumes; 15 for the archival copy and 16 for the review copy.

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Fexofenadine Hydrochloride Tablets, 180 mg manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, Allegra® (fexofenadine hydrochloride) Tablets, 180 mg under both fasting and post-prandial conditions. This application also contains a request for waiver of evidence of bioequivalence for the 30 mg and 60 mg tablet strengths.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

RECEIVED
JUL 0 1 2002
OGD / CDER

ANDA 76-447

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

AUG 26 2002

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Fexofenadine Hydrochloride Tablets,
30 mg, 60 mg, and 180 mg

DATE OF APPLICATION: June 28, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 1, 2002

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sarah Kim
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-447

cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB Davis 20-AUG-2002 date
HFD-615/ACamphire, CSO Lorianne Camphire date 8/19/02
Word File
V:\FIRMSNZ\Teva\LTRS&REV\76447.ACK
F/T EEH 08/19/02

ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 15, 2002

PATENT AMENDMENT

NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,632

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for Fexofenadine Hydrochloride Tablets with the purpose of providing an additional patent certification statement. U.S. Patent No. 6,399,632, which on its face has been assigned to Merrell Pharmaceuticals Inc., has listed in the Patent Term Extension and New Patents Docket Number 95S-0117 (October 11, 2002) for the reference listed product Allegra® Tablets. Therefore, TEVA wishes to provide the enclosed certification with regard to this patent. A copy of the listing in the above-mentioned docket is also provided for your reference.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
OCT 15 2002
OGD / CDER

NAI
3/7/03

12/2/02

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

NC

November 26, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT-
PATENT INFORMATION

ANDA #76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg, and 180 mg
UNSOLICITED AMENDMENT- REVISED PATENT CERTIFICATION

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an unsolicited amendment to the above-referenced pending ANDA for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg. The purpose of this amendment is to provide a revised patent certification statement for this product. Please note that TEVA's certification now contains Paragraph IV certification to U.S. Patent 5,932,247, U.S. Patent 5,855,912 and U.S. Patent 6,113,942. As such, we commit to provide notice to Aventis Pharmaceuticals (the NDA and patent owner) as required by 505(j)(2)(B)(i) and (ii) and to provide follow up to the Agency regarding receipt of notice, the 45-day period and status of the outcome of such notice.

We look forward to your continued review of ANDA #76-447. Should you have any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
NOV 27 2002
OGD / CDER

11/26/02

BIOEQUIVALENCY AMENDMENT

ANDA 76-447

DEC 11 2002

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Teva Pharmaceuticals USA TEL: 215-591-3000

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on June 28, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fexofendadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

DEC 11 2002

BIOEQUIVALENCY DEFICIENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:74-447 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg.

The Division of Bioequivalence has completed its review of your submission and the following deficiencies have been identified:

The Division of Bioequivalence requests that dissolution testing should be conducted under the following conditions:

Apparatus:	USP Apparatus II (Paddle) at 50 rpm
Medium:	900 mL 0.001 N HCl (30 and 60 mg)
	1800 mL 0.001 N HCl (180 mg)
Sampling Times:	10, 20, 30 and 45 minutes.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

ANDA 76-447

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

DEC 20 2002

TO: APPLICANT: TEVA Pharmaceuticals USA TEL: 215.591.3141

ATTN: Philip Erickson FAX: 215.591.8812

FROM: Craig Kiester PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 28, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fexofenadine Hydrochloride Tablets.

Reference is also made to your amendment(s) dated: October 15, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

CK 12/20/02

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

12/20/2002 FDA FAX

8. [redacted]

9. [redacted]

10. [redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available room temperature stability data for the product in the proposed packaging systems.

2. The drug substance and drug product are not compendial. Therefore, method validation is required. Once the deficiencies pertaining to this topic are satisfied, a method validation package will be sent for evaluation.

3. The Division of Bioequivalence has previously communicated deficiencies to you. Please respond with your amendment regarding these deficiencies.

4. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.

5. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

TEVA

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3141
FAX: (215) 591 8812

January 8, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT-
PATENT INFORMATION

NEW CORRESP
NC

ANDA #76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
UNSOLICITED AMENDMENT- REVISED PATENT CERTIFICATION

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an unsolicited amendment to the above-referenced pending ANDA for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg. The purpose of this amendment is to provide a revised patent certification statement for this product. Please note that TEVA's certification now contains Paragraph IV certification to U.S. Patent 5,578,610, U.S. Patent 5,855,912, U.S. Patent 5,932,247, U.S. Patent 6,037,353, U.S. Patent 6,113,942, U.S. Patent 6,187,791 and U.S. Patent 6,399,632. As such, we commit to provide notice to Aventis Pharmaceuticals (the NDA and patent owner) as required by 505(j)(2)(B)(i) and (ii) and to provide follow up to the Agency regarding receipt of notice, the 45-day period and status of the outcome of such notice.

We look forward to your continued review of ANDA #76-447. Should you have any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

RECEIVED
JAN 0 9 2003
OGD / CDER

NAZ
3/7/03

Author NAZ 2/26/03

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.PH.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

NEW CORRESP
NC

February 14, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT-
PATENT INFORMATION

ANDA #76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
UNSOLICITED AMENDMENT- UPDATED PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an unsolicited amendment to the above-referenced pending ANDA for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg. The purpose of this amendment is to provide an updated patent certification and exclusivity statement in recognition of the awarding of pediatric exclusivity as listed in the Patent Term Extension and New Patents Dockets Number *95S-0117 (February 11, 2003). Please note, this updated certification does not add any additional patents nor alters certification to any previously listed patents, but merely acknowledges the extension offered by the pediatric exclusivity. Therefore, the date of our original certification to the listed patents remains unchanged. A copy of the listing in the above-mentioned docket is also provided for your reference.

We look forward to your continued review of ANDA #76-447. Should you have any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/cw
Enclosures

RECEIVED
FEB 20 2003
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

March 20, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

DRUG AMENDMENT
N/AB

BIOEQUIVALENCY AMENDMENT

ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg, and 180 mg
BIOEQUIVALENCY AMENDMENT – RESPONSE TO DECEMBER 11, 2002 COMMENTS

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above referenced pending ANDA in accord with a December 11, 2002 review letter. For ease of review, please find attached a copy of this letter **(Attachment 1)**. The subject of this amendment is our response to the request to provide dissolution testing results incorporating the dissolution testing parameters specified in the December 11, 2002 correspondence.

Please find enclosed, as **Attachment 2**, a new Dissolution Method (Method No. SI-17382, Ed. No. 01), which incorporates the dissolution testing parameters contained in your December 11, 2002 correspondence. Specifically the medium has been changed from [redacted] to 0.001N HCl. Please note, this method was based upon the Dissolution Method (Method No. SI-17054, Ed. No. 03) previously submitted in the original application and contains the change in dissolution medium along with minor format changes. Please note that this method only corresponds to the dissolution testing performed in response to your request for Comparative Dissolution Profiles incorporating the requested dissolution parameters and sampling times, for the 30 mg, 60 mg, and 180 mg strengths **(Attachment 3)**. Prior to implementation of the aforementioned dissolution parameters, we await the completion of your review and your guidance regarding the conditions and specifications to be incorporated into the release and stability requirements for this drug product.

This information is submitted for your review and approval. If there are any questions, or if additional information is needed, please do not hesitate to call me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

RECEIVED
MAR 2 1 2003
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

April 1, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

NEW CORRESP
NC

NAI
R.R. 4.1AS w/t.
6/23/03

ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT / END OF 45-DAY CLOCK / LEAGAL STATUS – US PATENT Nos. 5,578,610, 5,855,912, 5,932,247, 6,037,353, 6,113,942, 6,187,791 and 6,399,632

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement for U.S. Patent Nos. 5,578,610, 5,855,912, 5,932,247, 6,037,353, 6,113,942, 6,187,791 and 6,399,632 was provided to Aventis Pharmaceuticals Inc., as the holder of NDA # 20-872 for Allegra® (fexofenadine hydrochloride tablets), 30 mg, 60 mg and 180 mg and owner of U.S. Patent Nos. 5,855,912 and 6,113,942, AMR Technology, Inc. as the owner of U.S. Patent No. 5,578,610, Carderm Capital L.P. as the owner of U.S. Patent Nos. 6,187,791 and 6,399,632, Merrell Pharmaceuticals Inc. as the owner of U.S. Patent No. 6,037,353, and Hoechst Marion Roussel, Inc. as the owner of U.S. Patent No. 5,932,247, in accord with 314.95(c).

In accord with 21 CFR 314.95(e), TEVA Pharmaceuticals USA is hereby providing documentation of the receipt of Notice of Certification for U. S. Patent Nos. 5,578,610, 5,855,912, 5,932,247, 6,037,353, 6,113,942, 6,187,791 and 6,399,632 (**Attachment 1**). Notice was received by AMR Technology, Inc. on January 17, 2003, by Aventis Pharmaceuticals Inc. on January 20, 2003, by Carderm Capital L.P. on January 20, 2003, by Merrell Pharmaceuticals Inc. on January 21, 2003 and by Hoechst Marion Roussel, Inc. on February, 11, 2003. In accord with 314.95(f), the first day of the 45-day period provided for in Section 505(j)(4)(B)(iii) of the Act is February 12, 2003, the first day after the receipt of Notice. Therefore, the 45-day period ended on March 28, 2003.

We hereby inform the Agency of a suit filed by Aventis Pharmaceuticals Inc., Merrell Pharmaceuticals Inc. and Carderm Capital L.P. against TEVA concerning U.S. Patent Nos. 5,738,872; 6,037,353; 6,399,632; 6,187,791; 5,855,912 and 6,113,942 (please note that the '872 patent is not listed in the Orange Book and therefore TEVA was not required to certify to it). The suit, Civil Action No. 03CV487, was filed on February 3, 2003 in the District Court of New Jersey. The aforementioned suit was filed within the 45-day period. A copy of the complaint is provided as **Attachment 2**.

No action for the infringement of U.S. Patent No. 5,578,610 within the meaning of section 505(j)(5)(B)(iii) of the Act was brought against TEVA within the 45-day period. Resultant from AMR Technology, Inc. failing to undertake legal action within the 45-day period, they have waived their right to pursue future legal endeavors under the scope of the Waxman-Hatch Act regarding this patent.

No action for the infringement of U.S. Patent No. 5,932,247 within the meaning of section 505(j)(5)(B)(iii) of the Act was brought against TEVA within the 45-day period. Resultant from Hoechst Marion Roussel, Inc. failing to undertake legal action within the 45-day period, they have waived their right to pursue future legal endeavors under the scope of the Waxman-Hatch Act regarding this patent.

TEVA hereby commits to provide notification of the outcome of the above noted suit in appropriate submissions to this application.

If there are any questions regarding the information presented herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

July 8, 2004

MINOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N/A pm

ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
MINOR AMENDMENT - RESPONSE TO DECEMBER 20, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated December 20, 2002. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the correspondence.

A. Deficiencies

1. [redacted]

2. [redacted]

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

7/8/2004 TEVA LETTER

4. We note and acknowledge that our labeling is pending review and that any deficiencies will be communicated under separate cover.

5. We note and acknowledge that the firms referenced in our ANDA relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

In addition, we are providing a revised exclusivity statement (**Attachment 15**) for the purpose of acknowledging the listing of the M-25 exclusivity and its corresponding Pediatric Exclusivity granted for the reference listed drug, Allegra® Tablets. The M-25 exclusivity pertains to the additional safety and PK information in children 6 months to less than 6 years of age added to the package insert. Please note that we will not include this indication in our labeling until expiration of the M-25 exclusivity and its corresponding Pediatric Exclusivity. However, in accord with the Best Pharmaceuticals for Children Act, we have included a replacement statement that acknowledges the innovator's exclusivity. Therefore, we are providing revised draft labeling. Please find enclosed, 4 copies of TEVA's draft package insert (**Attachment 16**), 4 copies of draft container labels for each strength and packaging configuration (**Attachment 17**), and a comparison (**Attachment 18**) of the draft package insert and the draft container labels to those last submitted. Please note that the storage conditions on the container labels were revised in accordance with our current format. In addition, enclosed as **Attachment 19**, we have provided an electronic version of our labeling in accord with 21 CFR 314.94(d) requiring mandatory electronic submission of labeling effective June 8, 2004.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

MINOR AMENDMENT

ANDA 76-447

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
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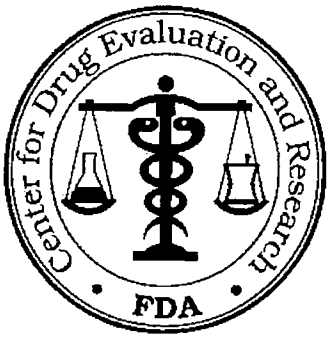
SEP 29 2004



APPLICANT: TEVA Pharmaceuticals, USA TEL: 215.591.3141

ATTN: Philip Erickson FAX: 215.591.8812

FROM: Simon Eng PROJECT MANAGER: (301) 827-5765

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 28, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fexofenadine Hydrochloride Tablets, 30 mg, 60 mg, and 180 mg.

Reference is also made to your amendment dated July 8, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachment (___1_ page). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

9/28/04

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information from

9/29/2004 FDA FAX

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

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philip.erickson@tevausa.com

January 5, 2005

ORIG AMENDMENT
N/AF

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT - LABELING

ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
MINOR AMENDMENT (LABELING) – RESPONSE TO DECEMBER 8, 2004 EMAIL

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to a December 8, 2004 email contact with Debra Catterson of the Agency's Division of Labeling and Program Support. Specifically, we were asked to update our insert in accord with the text provided in the aforementioned email. This text is considered to be consistent with the "Best Pharmaceuticals Act for Children". Additionally, we were asked to provide final print labeling for both container labels and insert labeling.

Please find enclosed, as **Attachment 1**, the final printed container labels for each strength, along with a comparison to that of our last submitted container labels.

In accord with the supplied text provided in the December 8, 2004 email contact, please find enclosed as **Attachment 2**, a CD containing an electronic version of our final printed insert in PDF format along with a comparison between the revised insert and our last submitted version. For ease of your review, a draft version of the insert, identical in text to the final print version, is also provided in Word format. In accord with December 8, 2004 email, the CD also contains a comparison of our final printed insert as compared to the labeling text provided in the aforementioned email. Please note that due to formatting issues, the comparison improperly indicates that the tables contained within the labeling text have been replaced. Please note the submission of the electronic labeling is in accord with 21 CFR 314.94(d) requiring mandatory electronic submission of labeling effective June 8, 2004.

Please note, all patents and exclusivities currently listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") have been addressed in previous correspondences to this application

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JAN 06 2005

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned email contact. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

RE/jmd
Enclosures

APPEARS THIS WAY
ON ORIGINAL

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February 3, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

UNSOLICITED AMENDMENT - LABELING

N/AF

ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
UNSOLICITED AMENDMENT – REVISED LABELING

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced, pending Abbreviated New Drug Application. Specifically, we have corrected the list of inactive ingredients contained within our insert. Please note that upon further review, our previously submitted insert inadvertently included ——————— and ——————— amongst the list of inactive ingredients. Since these two inactive ingredients are not part of our proposed formulation, they have been removed from our insert's list of inactive ingredients. Please note this is the only change made to the insert since our last submitted insert, supplied in our minor amendment (labeling) dated January 5, 2005.

Please find enclosed, a CD containing an electronic version of our final printed insert in PDF format along with a comparison between the revised insert and our last submitted version. For ease of your review, a draft version of the insert, identical in text to the final print version, is also provided in Word format. Please note the submission of the electronic labeling is in accord with 21 CFR 314.94(d) requiring mandatory electronic submission of labeling effective June 8, 2004.

This information is submitted for your continued review and approval of this ANDA. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

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February 22, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT

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ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
MINOR AMENDMENT - RESPONSE TO SEPTEMBER 29, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated September 29, 2004. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the correspondence.

A. Deficiencies

1. [redacted]

2. [redacted]

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information from

9/29/2004 TEVA LETTER

B. Notes and Acknowledgements

1. We note and acknowledge that our labeling information is pending review and that any deficiencies will be communicated separately. Please note, our response to a December 8, 2004 email contact from Debra Catterson of the Agency's Division of Labeling and Program Support, was provided in the form of a minor amendment (labeling) dated January 5, 2005. Additionally, we submitted an unsolicited amendment (labeling) dated February 3, 2005, in which we provided an electronic version of our revised final printed insert.

2. We note and acknowledge that a satisfactory compliance evaluation of the firms referenced in the ANDA is required for approval.

We are aware of proposed monographs for both the drug substance and drug product as presented in USP PF 30(4 & 6). Please note that we have been informed via a communication from Dr. ——— that the USP Council of Experts is scheduled to meet this week to discuss the postponement of the Fexofenadine HCl monograph that was published in USP28-NF23 Supp l, pp 3327 – 3328. The Council's decision could mean that the monograph would not become effective on April 1, 2005. Additionally, we have submitted a petition to PF 30(6) today with regard to the proposed Fexofenadine HCl Tablet Related Compound monograph. A copy of that Petition is enclosed as Attachment 6 for your convenience.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

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Philip Erickson, R.Ph.
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Solid Oral Dosage Forms

ORIG AMENDMENT
NAM

March 22, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

UNSOLICITED AMENDMENT

ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
UNSOLICITED AMENDMENT – ALTERNATE SITE OF API MANUFACTURE

Dear Mr. Buehler:

Teva Pharmaceuticals USA submits herewith an unsolicited amendment to the above referenced pending Abbreviated New Drug Application. This amendment is provided to propose the use of an alternate manufacturing site —— of the active ingredient, fexofenadine hydrochloride in addition to the original —— API site. We have been informed by the API manufacturer, ——————————, that they intended to utilize the alternate facility under their corporate domain for the manufacturing of this compound. The proposed facility has been identified as:

[ ]

In support of this alternate facility the following documents are provided:

1) An updated Letter of Authorization to reference —————— DMF, # ——, which has been amended to included information relating to the alternate site of manufacture. Additionally, we provide a copy of a correspondence from —————— establishing that the ——— ——— utilized at the proposed site is unchanged and that the proposed site is GMP compliant and has been inspected by the Agency. **(Attachment 1)**

2) A summary table providing comparison of raw material test specifications and results of material manufactured at each site. **(Attachment 2)**

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3) Teva and manufacturer's certificates of analysis providing test results for material manufactured at each site. The results of this testing established that the material manufactured at the proposed —— site is comparable to that manufactured at the original —— site. **(Attachment 3)**

Teva Pharmaceuticals USA commits to place the first commercial batch of finished product manufactured using API from the proposed —— site on controlled room temperature stability. The data generated from this stability study will be provided in annual reports made to this application.

This information is submitted towards the continued review and approval of the pending Abbreviated New Drug Application. If there are any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/rsv
Enclosures

Administrative Offices:
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April 26, 2005

ORIG AMENDMENT
N/AM

TELEPHONE AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS, 30 mg, 60 mg and 180 mg
TELEPHONE AMENDMENT - RESPONSE TO APRIL 20, 2005 TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced, pending Abbreviated New Drug Application in response to our April 20, 2005 telephone contact with Simon Eng of your Office. Specifically, we were asked _____

In accord with your request, we have _____ as follows:

_____

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It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned telephone contact. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

APPEARS THIS WAY
ON ORIGINAL

Administrative Offices:
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ORIG AMENDMENT

June 7, 2005

Gary Buehler, Director
Office of Generic Drugs
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Metro Park North II
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TELEPHONE AMENDMENT

ANDA 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS 30 mg, 60 mg, and 180 mg
TELEPHONE AMENDMENT – RESPONSE TO JUNE 1, 2005 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA in response to a request made by Simon Eng of your Office on June 1, 2005. Specifically, we are providing a revised analytical method for the ——————————. Please note that while the proposed —————————— has not changed, clarification has been added to indicate that once the —————————— must be completed ——————. Please note that in conjunction with this change, the method now requires that the——————————. Enclosed, please find revised Analytical Method RM-0317.

This information is submitted for your review and approval of ANDA 76-447. Should you have any questions or comments, please do not hesitate to contact me via telephone at (215)591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/PE

PE
Enclosure

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Administrative Offices:
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Deborah A. Jaskot, M.S., RAC
Vice President, Regulatory Affairs

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ORIG AMENDMENT

August 31, 2005

Gary Buehler, Director
Office of Generic Drugs
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Document Control Room
Metro Park North II
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Rockville, MD 20855-2773

REQUEST FOR IMMEDIATE FINAL APPROVAL

ANDA 76-447
FEXOFENADINE HYDROCHLORIDE TABLETS 30 mg, 60 mg, and 180 mg
MINOR AMENDMENT – REQUEST FOR FINAL APPROVAL

Dear Mr. Buehler:

We submit herewith a request for immediate final approval of ANDA 76-447. This request is made in conjunction with a selective waiver of 180 day exclusivity from the holder of ANDA 76-191, Barr Laboratories, Inc. to Teva Pharmaceuticals USA. A copy of this waiver request is provided herein for your reference. Please note that Teva's ANDA 76-447 was granted tentative approval on July 19, 2005 and no changes have been made to this product or its labeling since the tentative approval was granted. Since the 30 month stay of approval ended on July 14, 2005, Teva's ANDA would have been eligible for final approval on July 19, 2005 but for Barr's entitlement to exclusivity. Therefore immediate final approval may be granted in light of Barr's selective waiver request.

Should you have any questions or comments, please do not hesitate to contact me via telephone at (215) 591-3142 or via facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DAJ/sjp
Enclosure

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