Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amounts of fexofenadine hydrochloride (C_{32}H_{39}NO_4 · HCl) and pseudoephedrine hydrochloride (C_{10}H_{15}NO · HCl).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

Add the following:

*Labeling—When more than one Dissolution test is given, the labeling states the test used only if Test 1 is not used.

USP Reference standards (11)—USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound A RS. USP Pseudoephedrine Hydrochloride RS.

Change to read:

Identification—

A: \( \text{USP Fexofenadine Hydrochloride RS} \) The retention times of the major peaks in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay.

B: \( \text{USP Fexofenadine Hydrochloride RS} \) Thin-Layer Chromatographic Identification Test (201)—A

Adsorbent: 0.2-mm layer of high-performance thin-layer chromatographic silica gel mixture. Dry the plate at 105°C for one hour before use.

Test solution—Weigh and finely powder not fewer than 4 Tablets. Transfer powdered Tablets, equivalent to 30 mg of fexofenadine hydrochloride and 60 mg of pseudoephedrine hydrochloride, into a suitable vessel, and add 5 mL of methanol. Cap the vessel, and shake vigorously for about 2 minutes. Pass the resulting suspension through a suitable 0.45-μm filter. Use the filtrate.

Fexofenadine hydrochloride standard solution—Dissolve an accurately weighed quantity of USP Fexofenadine Hydrochloride RS in methanol to obtain a solution having a known concentration of about 6 mg per mL.

Pseudoephedrine hydrochloride standard solution—Dissolve an accurately weighed quantity of USP Pseudoephedrine Hydrochloride RS in methanol to obtain a solution having a known concentration of about 12 mg per mL.

Application volume: 10 μL.

Developing solvent solution: a mixture of toluene, dehydrated alcohol, and ammonium hydroxide (50:45:5).

Procedure—Proceed as directed in the chapter, using the Developing solvent system. After removal of the plate, mark the solvent front, and allow the plate to air-dry. Heat the plate at 105°C until the odor of ammonia disappears (approximately 5 minutes). Allow the plate to cool, and examine under UV light at 254 nm. The \( R_f \) values are about 0.17 for fexofenadine and 0.39 for pseudoephedrine. The \( R_f \) value of fexofenadine hydrochloride in the test sample is comparable to that of fexofenadine hydrochloride in the Standard solution. The \( R_f \) value of pseudoephedrine hydrochloride in the test sample is comparable to that of pseudoephedrine hydrochloride in the Standard solution.

Change to read:

Dissolution (711)—

*TEST 1—

Medium: 0.001 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Times: fexofenadine hydrochloride: 15 and 45 minutes; pseudoephedrine hydrochloride: 45 minutes; 3, 5, and 12 hours.

Determine the percentages of the labeled amounts of fexofenadine hydrochloride (C_{32}H_{39}NO_4 · HCl) and of pseudoephedrine hydrochloride (C_{10}H_{15}NO · HCl) dissolved by using the following method.

Buffer solution—Dissolve 14.0 g of monobasic sodium phosphate monohydrate in 2 L of water. Adjust with 85% phosphoric acid to a pH of 2.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (55:45). Make adjustments if necessary (see System Suitability under Chromatography (621)).

Standard solution—[NOTE—A small amount of methanol, not to exceed 0.5% of the total volume, can be used to dissolve the fexofenadine hydrochloride.] Dissolve accurately weighed quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in Medium, and dilute quantitatively, and stepwise if necessary, to obtain a solution containing known concentrations similar to those expected in the solution under test.

Test solution—Use portions of the solution under test passed through a 0.45-μm nylon filter.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm x 25-cm column containing packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the resolution, \( R_f \), between fexofenadine and pseudoephedrine is not less than 3.0; the tailing factor is not more than 1.5 for fexofenadine and for pseudoephedrine; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 μL) of the Standard solution and the Test solution into the chromatograph, and record the peak responses for fexofenadine and pseudoephedrine. Calculate the amounts of fexofenadine hydrochloride (C_{32}H_{39}NO_4 · HCl) and pseudoephedrine hydrochloride (C_{10}H_{15}NO · HCl) dissolved.

Tolerances—For fexofenadine hydrochloride (C_{32}H_{39}NO_4 · HCl), not less than 65% (\( Q \)) of the labeled amount is dissolved in 15 minutes and not less than 80% (\( Q \)) of the labeled amount is dissolved in 45 minutes; the percentages of the labeled amount of pseudoephedrine hydrochloride (C_{10}H_{15}NO · HCl) dissolved at the times specified conform to Acceptance Table 2 under Dissolution (711).

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount dissolved (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 minutes</td>
<td>not more than 36%</td>
</tr>
<tr>
<td>3 hours</td>
<td>between 45% and 69%</td>
</tr>
<tr>
<td>5 hours</td>
<td>between 61% and 80%</td>
</tr>
<tr>
<td>12 hours</td>
<td>not less than 80%</td>
</tr>
</tbody>
</table>

*TEST 2—If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 2.

Medium: 0.001 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Times: fexofenadine hydrochloride: 45 minutes; pseudoephedrine hydrochloride: 30 minutes; 2, 4, and 12 hours.

Determine the percentages of the labeled amounts of fexofenadine hydrochloride (C_{32}H_{39}NO_4 · HCl) and of pseudoephedrine...
hydrochloride (C₁₀H₁₅NO · HCl) dissolved by using the following method.

**Buffer solution**—Dissolve about 2.7 g of monobasic potassium phosphate and 2.2 g of sodium 1-octanesulfonate in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.50 ± 0.05.

**Mobile phase**—Prepare a filtered and degassed mixture of Buffer solution, methanol, and acetonitrile (4:3:3). Make adjustments if necessary (see System Suitability under Chromatography (621)).

Fexofenadine standard stock solution—Transfer about 66 mg, accurately weighed, of USP Fexofenadine Hydrochloride RS to a 100-mL volumetric flask. Add 10 mL of methanol, and swirl until dissolved. Add about 50 mL of Medium, and mix. Allow the solution to equilibrate to room temperature, and dilute with Medium to volume.

Pseudoephedrine standard stock solution—Transfer about 66 mg, accurately weighed, of USP Pseudoephedrine Hydrochloride RS to a 100-mL volumetric flask. Add 10 mL of methanol, and swirl until dissolved. Add about 50 mL of Medium, and mix. Allow the solution to equilibrate to room temperature, and dilute with Medium to volume.

Working standard solution—Transfer 10.0 mL of Fexofenadine standard stock solution and 20.0 mL of Pseudoephedrine standard stock solution to a 100-mL volumetric flask, dilute with Medium to volume, and mix.

**Test solution**—Pass a portion of the solution under test through a suitable filter having a porosity of 0.45 µm.

**Chromatographic system**—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column containing 5-µm packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the Working standard solution, and record the peak responses as directed for Procedure: the resolution, R, between fexofenadine and pseudoephedrine is not less than 2.0; the tailing factor for the fexofenadine peak is not more than 2.0, and for the pseudoephedrine peak, not more than 2.5; and the relative standard deviation for replicate injections for both peaks is not more than 2.0%.

**Procedure**—Separately inject equal volumes (about 10 µL) of the Working standard solution and the Test solution into the chromatograph, and record the peak responses for fexofenadine and pseudoephedrine. Calculate the amounts of fexofenadine hydrochloride (C₃₂H₄₉NO₄ · HCl) and pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved.

**Tolerances**—For fexofenadine hydrochloride (C₃₂H₄₉NO₄ · HCl), not less than 80% (Q) of the labeled amount is dissolved in 45 minutes; and the percentages of the labeled amount of pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved at the times specified conform to Acceptance Table 2 under Dissolution (711).* 

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount dissolved (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 minutes</td>
<td>not more than 35%</td>
</tr>
<tr>
<td>2 hours</td>
<td>between 38% and 58%</td>
</tr>
<tr>
<td>4 hours</td>
<td>between 56% and 76%</td>
</tr>
<tr>
<td>12 hours</td>
<td>not less than 80%</td>
</tr>
</tbody>
</table>

*TEST 3—If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 3.

**Medium:** 0.001 N hydrochloric acid; 900 mL.

**Apparatus 2:** 50 rpm.

Times: fexofenadine hydrochloride: 30 minutes; pseudoephedrine hydrochloride: 1, 3, 5, and 12 hours.

Determine the percentages of the labeled amounts of fexofenadine hydrochloride (C₃₂H₄₉NO₄ · HCl) and of pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved by using the following procedure.

**Buffer solution**—Dissolve 6.64 g of monobasic sodium phosphate in 1000 mL of water, adjust to a pH of 2.50 ± 0.05 with phosphoric acid.

**Mobile phase**—Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (3:2). Make adjustments if necessary (see System Suitability under Chromatography (621)).

**Standard solution**—[NOTE—A small amount of methanol, not exceeding 0.5% of the final total volume, can be used to dissolve fexofenadine hydrochloride.] Dissolve accurately weighed quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in Medium, and dilute quantitatively, and step-wise if necessary, to obtain a solution containing known concentrations similar to those expected in the solution under test.

**Test solution**—Pass a portion of the solution under test through a PVDF or nylon 0.45-µm filter.

**Chromatographic system**—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column containing packing L1. The flow rate is about 2.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 for fexofenadine and pseudoephedrine; and the relative standard deviation for replicate injections is not more than 2.0%.

**Procedure**—Separately inject equal volumes (about 10 µL) of the Standard solution and the Test solution into the chromatograph, and record the peak responses for fexofenadine and pseudoephedrine. Calculate the amounts of fexofenadine hydrochloride (C₃₂H₄₉NO₄ · HCl) and pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved.

**Tolerances**—For fexofenadine hydrochloride (C₃₂H₄₉NO₄ · HCl), not less than 80% (Q) of the labeled amount is dissolved in 30 minutes; the percentages of the labeled amount of pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved at the times specified conform to Acceptance Table 2 under Dissolution (711).* 

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Amount dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>between 10% and 35%</td>
</tr>
<tr>
<td>3</td>
<td>between 25% and 55%</td>
</tr>
<tr>
<td>5</td>
<td>between 40% and 65%</td>
</tr>
<tr>
<td>12</td>
<td>not less than 65%</td>
</tr>
</tbody>
</table>

* (RB 2-Nov-2009)

**TEST 4**—For products labeled with a dosing interval of 24 hours. If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 4.

**Medium:** 0.001 N hydrochloric acid; 900 mL.

**Apparatus 2:** 50 rpm.

Times: fexofenadine hydrochloride: 30 minutes; pseudoephedrine hydrochloride: 3, 7, and 23 hours.

Determine the percentages of the labeled amounts of fexofenadine hydrochloride (C₃₂H₄₉NO₄ · HCl) and of pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved by using the chromatographic procedure described in Test 1.

**Tolerances**—For fexofenadine hydrochloride (C₃₂H₄₉NO₄ · HCl), not less than 80% (Q) of the labeled amount is dissolved in 30 minutes; the percentages of the labeled amount of pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved at the times specified conform to Acceptance Table 2 under Dissolution (711).
Uniformity of dosage units (905): meet the requirements.

Change to read:

Related compounds—

Buffer solution, Mobile phase, System suitability preparation, and Chromatographic system—Proceed as directed in the Assay.

Standard solution—Use the Standard preparation, prepared as directed in the Assay.

Reference solution—Use the Assay stock preparation, prepared as directed in the Assay.

Chromatographic system (see Chromatography (621))—Chromatograph the System suitability preparation as directed for Procedure: the relative retention times are about 1.2 for ephedrine and 1.0 for pseudoephedrine; the resolution, R, between pseudoephedrine and ephedrine is not less than 1.7; and the relative standard deviation for replicate injections is not more than 1.0% based on the pseudoephedrine peak. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.2 for fexofenadine related compound A, 3.1 for decarboxylated degradant, and 1.0 for fexofenadine; the resolution, R, between fexofenadine and fexofenadine related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 1.0% based on the fexofenadine peak and not more than 3.0% based on the individual peaks for fexofenadine related compound A and decarboxylated degradant.

Procedure—Separately inject equal volumes (about 20 μL) of the Test solution and the Reference solution into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of fexofenadine related compound A and decarboxylated degradant in the portion of Tablets taken by the formula:

\[
100(C_S / C_T)\cdot(r_S / r_T)
\]

in which C_S is the concentration, in mg per mL, of either USP Fexofenadine Related Compound A RS or decarboxylated degradant in the Standard solution; C_T is the nominal concentration, in mg per mL, of fexofenadine hydrochloride in the Test solution; r_S is the individual peak area of either fexofenadine related compound A or decarboxylated degradant obtained from the Test solution; and r_T is the peak area of fexofenadine related compound A obtained from the Standard solution. Calculate the percentage of ephedrine in the portion of Tablets taken by the formula:

\[
100(F\cdot C_S / C_T)\cdot(r_S / r_T)
\]

in which F is the relative response factor for ephedrine (F is 0.394); C_S is the concentration, in mg per mL, of USP Pseudoephedrine Hydrochloride RS in the Standard solution; C_T is the nominal concentration, in mg per mL, of pseudoephedrine hydrochloride in the Test solution; r_S is the peak height for ephedrine obtained from the Test solution; and r_T is the peak height for pseudoephedrine obtained from the Standard solution. Calculate the percentage of any other impurities in the portion of Tablets taken by the formula:

\[
100r_S / (25r_S + r_T)
\]

in which r_S is the individual peak area response for an individual unknown impurity in the Test solution; 25 is the difference in concentration between the Test solution and the Reference solution; r_S is the peak area response for fexofenadine hydrochloride obtained from the Reference solution; and r_T is the sum of the peak area responses of all unknown impurities in the Test solution. Disregard any peak below 0.05%.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoephedrine</td>
<td>1.0</td>
<td>not more than 0.2%</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not more than 0.2%</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>1.0</td>
<td>not more than 0.4%</td>
</tr>
<tr>
<td>Fexofenadine related compound A</td>
<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not more than 0.2%</td>
</tr>
<tr>
<td>Decarboxylated degradant&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not more than 0.2%</td>
</tr>
<tr>
<td>Tertiary dehydrated impurity&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.8</td>
<td>not more than 0.2%</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>not more than 0.2%</td>
</tr>
<tr>
<td>∗∗ Total impurities</td>
<td>—</td>
<td>not more than 0.8%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Relative to pseudoephedrine.

<sup>b</sup>Relative to fexofenadine.

<sup>c</sup>[(+)-4-[(4-Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-2,2-dimethyl phenylhydroperoxide.

<sup>d</sup>[(+)-4-(4-(Diphenylmethylene)-1-piperidinyl)-1-hydroxybutyl]-2,2-dimethyl phenylhydroperoxide.

Change to read:

Assay—

Buffer solution—Dissolve 6.8 g of sodium acetate and 16.22 g of sodium 1-octanesulfonate in water, and dilute with water to 1 L. Adjust with glacial acetic acid to a pH of 4.6.

Mobile phase—Prepare a filtered and degassed mixture of methanol and Buffer solution (65 : 35). Make adjustments if necessary (see System Suitability under Chromatography (621)).

System suitability preparation—Transfer an accurately weighed quantity, about 40 mg, of USP Pseudoephedrine Hydrochloride RS to a 50-mL volumetric flask. Add 5 mL of tert-butylhydroperoxide solution, and sonicate. Cover the flask opening with aluminum foil, and place the flask in an oven at about 90° for 60 minutes. Remove from the oven, and allow to cool. Add 35 mL of Mobile phase, and cool to room temperature. Dilute with Mobile phase to volume, and mix. The degradation of pseudoephedrine hydrochloride by this process produces the related compound ephedrine.

Related compounds preparation—Dissolve accurately weighed quantities of USP Fexofenadine Related Compound A RS and decarboxylated degradant<sup>a</sup> in a volume of methanol, and dilute quantitatively, and stepwise if necessary, with Buffer solution to maintain a ratio of methanol and Buffer solution (60 : 40). Dilute quantitatively, and stepwise if necessary, with methanol and Buffer solution (60 : 40) to obtain a solution having known concentrations of 0.2 mg per mL for each component. Dilute 10.0 mL of this solution with Mobile phase to 100 mL to obtain a final solution having known concentrations of 0.02 mg per mL for each component.

Standard stock preparation—Dissolve accurately weighed quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having known concentrations of about 0.4 mg per mL and 0.8 mg per mL of fexofenadine hydrochloride<sup>a</sup> and pseudoephedrine hydrochloride<sup>a</sup>, respectively.

<sup>a</sup>Available from USP as USP Fexofenadine Related Compound C AS, Cat# 12704669-905.
**Fexofenadine**

**Standard preparation**—Dilute 6.0 mL of the Standard stock preparation and 15.0 mL of the Related compounds preparation with Mobile phase to 50 mL to obtain a solution having known concentrations of about 0.048 mg of fexofenadine hydrochloride per mL, 0.096 mg of pseudoephedrine hydrochloride per mL, 0.006 mg of fexofenadine related compound A per mL, and 0.006 mg of decarboxylated degradant per mL.

**Assay stock preparation**—Transfer not fewer than 10 whole Tablets to a 500-mL volumetric flask. Add 300 mL of methanol, and shake by mechanical means at high speed for 60 minutes. Sonicate the flask for 60 minutes at 40°. Add 150 mL of Buffer solution, and sonicate for 60 minutes at 40°. Vent the flask, and vigorously shake the flask by hand at 15-minute intervals during the mechanical shaking and sonication steps. Cool to room temperature, and dilute with Buffer solution to volume to obtain a solution containing approximately 1.2 mg of fexofenadine hydrochloride, 2.4 mg of pseudoephedrine hydrochloride, and 2.0 mg of decarboxylated degradant per mL. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

**Assay preparation**—Dilute 4.0 mL of the Assay stock preparation filtrate with Mobile phase to 100 mL. The final concentrations of fexofenadine hydrochloride, pseudoephedrine hydrochloride, and fexofenadine related compound A are 0.048 mg per mL and 0.096 mg per mL, respectively.

**Chromatographic system** (see Chromatography (621))—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 5-cm column that contains 5-µm packing L6 connected in series to a 4.6-mm × 25-cm column that contains 5-µm packing L11. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 35°. Chromatograph the System suitability preparation as directed for Procedure: the relative retention times are about 1.2 for ephedrine and 1.0 for pseudoephedrine; the resolution, R, between pseudoephedrine and ephedrine is not less than 1.7; and the relative standard deviation for replicate injections is not more than 1.0% based on the pseudoephedrine peak. Chromatograph the Standard preparation and record the peak responses as directed for Procedure: the relative retention times are about 1.2 for fexofenadine related compound A, 3.1 for decarboxylated degradant, and 1.0 for fexofenadine; the resolution, R, between fexofenadine and fexofenadine related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 1.0% based on the fexofenadine peak.

**Procedure**—Separately inject equal volumes (about 20 µL) of the Standard preparation and Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the fexofenadine and pseudoephedrine peaks. Calculate the percentage of the label claim of fexofenadine hydrochloride (C₁₇H₂₁NO₂·HCl) and pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl) in the portion of Tablets taken by the formula:

\[
100(C_S / C_T)(r_U / r_S)
\]

in which C_S is the concentration, in mg per mL, of either USP Fexofenadine Hydrochloride RS or USP Pseudoephedrine Hydrochloride RS in the Standard preparation; C_T is the nominal concentration, in mg per mL, of either fexofenadine hydrochloride or pseudoephedrine hydrochloride in the Assay preparation; and r_U and r_S are the peak responses obtained for either fexofenadine or pseudoephedrine from the Assay preparation and the Standard preparation, respectively.