**Olanzapine and Fluoxetine Capsules**

**DEFINITION**
Olanzapine and Fluoxetine Capsules contain an amount of Olanzapine and Fluoxetine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% each of the labeled amount of olanzapine (C\textsubscript{17}H\textsubscript{20}N\textsubscript{4}S) and fluoxetine (C\textsubscript{17}H\textsubscript{18}F\textsubscript{3}NO).

**IDENTIFICATION**
- The retention times of the major peaks of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.

**ASSAY**
- **PROCEDURE**

  **Buffer:** 37 mg/L of disodium ethylenediaminetetraacetate in water. Add 3.3 mL of phosphoric acid, and adjust with 50% sodium hydroxide to a pH of 2.5. Dissolve 8.7 g of sodium dodecyl sulfate in the resulting solution.

  **Mobile phase:** Acetonitrile and Buffer (1:1)
  **Standard solution:** 0.12 mg/mL of USP Olanzapine RS and 0.45 mg/mL of USP Fluoxetine Hydrochloride RS in Mobile phase

  **Sample solution:** Nominally, 0.06–0.18 mg/mL of olanzapine and 0.25–0.5 mg/mL of fluoxetine in Mobile phase from a counted number of Capsules prepared as follows. Place the Capsules (including shells) into a suitable volumetric flask and fill to about half volume with Mobile phase. Mix for NLT 30 min. If disintegration is incomplete, sonicate for NMT 5 min. Dilute with Mobile phase to volume, mix, and filter or centrifuge.

  **Chromatographic system**

  (See Chromatography (621), System Suitability.)

  **Mode:** LC
  **Detector:** UV 227 nm
  **Column:** 4.6-mm × 7.5-cm; 3.5-μm packing L7
  **Column temperature:** 40°
  **Flow rate:** 2 mL/min
  **Injection volume:** 10 μL
  **Run time:** 2.5 times the retention time of olanzapine

  **System suitability**

  **Sample:** Standard solution

  [NOTE—The relative retention times for olanzapine and fluoxetine are 1.0 and 1.5, respectively.]

  **Suitability requirements**

  **Resolution:** NLT 2.0 between olanzapine and fluoxetine

  **Relative standard deviation:** NMT 2.0% for the olanzapine and fluoxetine peaks

  **Analysis**

  **Samples:** Standard solution and Sample solution

  Calculate the percentage of the labeled amount of olanzapine (C\textsubscript{17}H\textsubscript{20}N\textsubscript{4}S) in the portion of Capsules taken:

  \[
  \text{Result} = \left( \frac{r_0}{r_1} \right) \times \left( \frac{C_0}{C_U} \right) \times 100
  \]

  \( r_0 \) = peak response of olanzapine from the Sample solution
  \( r_1 \) = peak response of olanzapine from the Standard solution
  \( C_0 \) = concentration of USP Olanzapine RS in the Standard solution (mg/mL)
  \( C_U \) = nominal concentration of olanzapine in the Sample solution (mg/mL)

  Calculate the percentage of the labeled amount of fluoxetine (C\textsubscript{17}H\textsubscript{18}F\textsubscript{3}NO) in the portion of Capsules taken:

  \[
  \text{Result} = \left( \frac{r_0}{r_3} \right) \times \left( \frac{C_0}{C_3} \right) \times \left( \frac{M_1}{M_2} \right) \times 100
  \]

  \( r_0 \) = peak response of fluoxetine from the Sample solution
  \( r_3 \) = peak response of fluoxetine from the Standard solution
  \( C_0 \) = concentration of USP Fluoxetine Hydrochloride RS in the Standard solution (mg/mL)
  \( C_3 \) = nominal concentration of fluoxetine in the Sample solution (mg/mL)
  \( M_1 \) = molecular weight of fluoxetine, 309.33
  \( M_2 \) = molecular weight of fluoxetine hydrochloride, 345.79

  **Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

- **Dissolution (711)**

  **Medium:** 0.1 N hydrochloric acid; 900 mL, deaerated. [NOTE—Helium sparging recommended.]

  **Apparatus 2:** 50 rpm, with 3-prong sinkers

  **Time:** 30 min for both olanzapine and fluoxetine

  **Standard solution:** USP Olanzapine RS and USP Fluoxetine Hydrochloride RS in Medium to obtain a final concentration of \( (L/1000) \) mg/mL each, where \( L \) is the Capsule label claim, in mg

  **Sample solution:** Pass a portion of the solution through a suitable filter of 0.45-μm pore size.

  **Buffer, Mobile phase, Chromatographic system, System suitability, and Analysis:** Proceed as directed in the Assay.

  Calculate the percentage of the labeled amount of olanzapine (C\textsubscript{17}H\textsubscript{20}N\textsubscript{4}S) dissolved:

  \[
  \text{Result} = \left( \frac{r_0}{r_{CS}} \right) \times \left( \frac{C_{S}}{C_{CS}} \right) \times \left( \frac{M_1}{M_2} \right) \times V \times 100
  \]

  \( r_0 \) = peak response of olanzapine from the Sample solution

  \( r_{CS} \) = peak response of olanzapine from the Standard solution

  \( C_{S} \) = concentration of USP Olanzapine RS in the Standard solution (mg/mL)

  \( C_{CS} \) = concentration of USP Fluoxetine Hydrochloride RS in Medium to obtain a final concentration of \( (L/1000) \) mg/mL each, where \( L \) is the Capsule label claim, in mg

  \( M_1 \) = molecular weight of fluoxetine, 309.33

  \( M_2 \) = molecular weight of fluoxetine hydrochloride, 345.79

  Calculate the percentage of the labeled amount of fluoxetine (C\textsubscript{17}H\textsubscript{18}F\textsubscript{3}NO) dissolved:

  \[
  \text{Result} = \left( \frac{r_0}{r_{CS}} \right) \times \left( \frac{C_{S}}{C_{CS}} \right) \times \left( \frac{M_1}{M_2} \right) \times V \times 100
  \]

  \( r_0 \) = peak response of fluoxetine from the Sample solution

  \( r_{CS} \) = peak response of fluoxetine from the Standard solution

  \( C_{S} \) = concentration of USP Fluoxetine Hydrochloride RS in the Standard solution (mg/mL)

  \( C_{CS} \) = concentration of USP Fluoxetine Hydrochloride RS in Medium to obtain a final concentration of \( (L/1000) \) mg/mL each, where \( L \) is the Capsule label claim, in mg

  \( M_1 \) = molecular weight of fluoxetine, 309.33

  \( M_2 \) = molecular weight of fluoxetine hydrochloride, 345.79

  **Volume of Medium:** 900 mL

  **Tolerances:** NLT 80% (Q) of the labeled amounts of olanzapine (C\textsubscript{17}H\textsubscript{20}N\textsubscript{4}S) and fluoxetine (C\textsubscript{17}H\textsubscript{18}F\textsubscript{3}NO) are dissolved.

- **Uniformity of Dosage Units (905):** Meet the requirements
**ORGANIC IMPURITIES**

**Change to read:**

**IMPURITIES**

- **System suitability solution:** 0.1 mg/mL of USP Olanzapine RS, 0.11 mg/mL of USP Fluoxetine Hydrochloride RS, and 0.002 mg/mL each of α[(2-methylamino)ethyl] benzyl alcohol, trifluoro-p-cresol, USP Fluoxetine Related Compound B RS, and USP Olanzapine Related Compound B RS in Mobile phase

- **Sample solution:** Empty the Capsules, and combine the contents in a suitable container. The contents of the Capsules may be powdered in a mortar, if necessary. Transfer an amount of the sample to a suitable volumetric flask to obtain nominally 0.2 mg/mL of olanzapine and 0.27–1.7 mg/mL of fluoxetine and fill to about 70% volume with Mobile phase. Mix for about 5 min. Dilute with Mobile phase to volume, mix, and filter or centrifuge.

- **Chromatographic system**
  - (See Chromatography (621), System Suitability.)
  - Mode: LC
  - Detector: UV 215 nm
  - Column: 4.6-mm × 25-cm; 5-µm packing L7
  - Temperatures:
    - Column: 35°
    - Autosampler: 5°
  - Flow rate: 1.5 mL/min
  - Injection volume: 50 µL
  - Run time: 1.5 times the retention time of fluoxetine

- **System suitability**
  - **Samples:** System suitability solution and Standard solution
  - **Suitability requirements**
    - **[NOTE—Identify the peaks using Table 1.]**

### Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α[(2-Methylamino)ethyl] benzyl alcohol</td>
<td>0.22</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Olanzapine related compound B</td>
<td>0.24</td>
<td>1.73</td>
<td>0.20</td>
</tr>
<tr>
<td>Trifluoro-p-cresol</td>
<td>0.30</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Fluoxetine related compound B</td>
<td>0.31</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fluoxetine related degradation product.

Olanzapine related degradation product.

Any other degradation product with a relative retention time <0.63 except fluoxetine related degradation products, and any degradation product with a relative retention time >1.0.

Sum of all specified fluoxetine related degradation products and any other fluoxetine related degradation product with relative retention times >1.0.

Sum of all specified olanzapine degradation products, any other degradation product with a relative retention time <0.63 except fluoxetine related degradation products, and any degradation product with relative retention time >1.0.

### Resolution

NLT 1.9 between α[(2-methylamino)ethyl] benzyl alcohol and olanzapine related compound B, System suitability solution

**Tailing factor:** NMT 1.8 for olanzapine and fluoxetine, System suitability solution and Standard solution

**Analysis**

**Samples:** Standard solution and Sample solution

**[NOTE—Peaks eluting before a relative retention time of 0.63 and after a relative retention time of 1.0, excluding any peak with relative retention times of 0.22, 0.30, and 0.31, are olanzapine related degradation products.]**

Calculate the percentage of each olanzapine related degradation product in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_i}{C_0} \right) \times \left( \frac{M_d}{M_s} \right) \times 100
\]

- \(r_d\) = peak response of each individual impurity from the Sample solution
- \(r_s\) = peak response of olanzapine from the Standard solution
- \(C_i\) = concentration of USP Olanzapine RS in the Standard solution (mg/mL)
- \(C_0\) = nominal concentration of olanzapine in the Sample solution (mg/mL)
- \(F\) = relative response factor (see Table 1)

**[NOTE—Peaks eluting at relative retention times of 0.22, 0.30, and 0.31, and any peaks between a relative retention time of 0.63 and 1.0, are fluoxetine related degradation products.]**

Calculate the percentage of each fluoxetine related degradation product in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_i}{C_0} \right) \times \left( \frac{M_d}{M_s} \right) \times 100
\]

- \(r_d\) = peak response of each individual impurity from the Sample solution
- \(r_s\) = peak response of fluoxetine from the Standard solution
- \(C_i\) = concentration of USP Fluoxetine Hydrochloride RS in the Standard solution (mg/mL)
 rhetorical question: The nominal concentration of fluoxetine in the sample solution (mg/mL) is \( C_u \).

- \( M_{r1} \): molecular weight of fluoxetine, 309.33
- \( M_{r2} \): molecular weight of fluoxetine hydrochloride, 345.79

Acceptance criteria: See Table 1.

### ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

- **USP Reference Standards (1)**

  USP Fluoxetine Hydrochloride RS  
  Benzenepropanamine, N-methyl-gamma-[4-(trifluoromethyl)phenoxy]-, hydrochloride, \( \pm \).  
  \( C_{17}H_{18}F_3NO \cdot HCl \)  
  345.79

  USP Olanzapine Related Compound B RS  
  N-Methyl-3-phenylpropylamine.  
  \( C_{10}H_{14}N \)  
  149.23

  USP Olanzapine RS  
  10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl).  
  \( C_{17}H_{20}N_4S \)  
  312.43

  USP Olanzapine Related Compound B RS  
  2-Methyl-10H-thieno-[2,3-b][1,5]benzodiazepin-4[5H]-one.  
  \( C_{12}H_{16}N_2O_S \)  
  230.29