Estradiol Transdermal System

Type of Posting                  Notice of Intent to Revise  
Posting Date                    28–Sep–2018              
Targeted Official Date          To Be Determined, Revision Bulletin 
Expert Committee                Chemical Medicines Monographs 5 

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 5 Expert Committee intends to revise the Estradiol Transdermal System monograph.

Based on the supporting documentation received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add Test 5 in the Drug Release section of the monograph.

- Drug Release Test 5 was validated using a Zorbax Eclipse XDB C18 brand of L1 column. A suitable guard column with L1 packing may also be used. The typical retention time for estradiol is about 2.3 min.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Gerald J. Hsu, Ph.D., Senior Scientific Liaison to the Chemical Medicines Monographs 5 Expert Committee (240-221-2097 or gdh@usp.org).

¹ This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
Estradiol Transdermal System

DEFINITION
Estradiol Transdermal System contains NLT 85.0% and NMT 120.0% of the labeled amount of estradiol (C_{18}H_{24}O_{2}).

IDENTIFICATION
• A. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY
• PROCEDURE
Diluent: Acetonitrile and water (1:1)
Mobile phase: Acetonitrile and water (55:45)
Standard solution: 0.1 mg/mL of USP Estradiol RS in Diluent
Sample solutions: Equivalent to 0.1 mg/mL of estradiol in Diluent, prepared as follows. Cut 10 Transdermal Systems into pieces, and keep the pieces from each system separate. Remove and discard the protective liners, if present, from the strips. Transfer the pieces of each system into separate stopped flasks of suitable size, and add a measured volume of Diluent to each flask to provide the target estradiol concentration. Shake by mechanical means for about 3 h, and sonicate for 15 min.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 15-cm; packing L1
Column temperature: 35°
Flow rate: 1 mL/min
Injection size: 25 µL

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.5%
Relative standard deviation: NMT 2.5%

Analysis
Samples: Standard solution and Sample solutions
Calculate the percentage of estradiol (C_{18}H_{24}O_{2}) in each Transdermal System taken:

Result = \left( \frac{r_{J}}{r_{S}} \right) \times \left( \frac{C_{J}}{C_{S}} \right) \times 100

where:
- \( r_{J} \) = peak response from the Sample solution
- \( r_{S} \) = peak response from the Standard solution
- \( C_{J} \) = concentration of USP Estradiol RS in the Standard solution (mg/mL)
- \( C_{S} \) = nominal concentration of estradiol in the Sample solution (mg/mL)

Use the individual assays to determine Uniformity of Dosage Units.
Acceptance criteria: 85.0%–120.0%

OTHER COMPONENTS
• ALCOHOL CONTENT (if present)
Diluent: Acetonitrile and water (1:1)
Internal standard solution: Prepare by diluting 4.0 mL of dehydrated methanol with water to 100 mL.
Standard stock solution: 5.0 mg/mL of ethanol in Diluent. Prepare by weighing by difference 1.6 mL of dehydrated alcohol into a tared 50-mL volumetric flask containing 15 mL of water, and dilute with Diluent to volume. Pipet 10.0 mL of this solution into a 50-mL volumetric flask, and dilute with Diluent to volume.
Standard solution: 2.5 mg/mL of ethanol. Prepare by pipetting 25.0 mL of the Standard stock solution into a 50-mL volumetric flask. Add 5.0 mL of the Internal standard solution, and dilute with water to volume.

Sample solutions: Prepare as directed for the Sample solutions in the Assay, with the following changes. Pipet 25.0 mL of each solution into individual 50-mL volumetric flasks. Add 5.0 mL of the Internal standard solution, and dilute with water to volume.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: GC
Detector: Flame ionization
Column: 2-mm × 2-m glass; support S2
Temperature
Column: 100°
Injection port: 200°
Detector: 200°
Carrier gas: Helium
Flow rate: 30 mL/min
Injection size: 2 µL

System suitability
Sample: Standard solution
[NOTE—The relative retention times for the methanol and alcohol peaks are 0.4 and 1.0, respectively.]

Suitability requirements
Relative standard deviation: NMT 1.5% from the peak response ratio of alcohol to methanol
Analysis
Samples: Standard solution and Sample solutions
Calculate the percentage of alcohol (C_{6}H_{12}O) in each Transdermal System taken:

Result = \left( \frac{R_{J}}{R_{S}} \right) \times \left( \frac{C_{J}}{C_{S}} \right) \times 100

where:
- \( R_{J} \) = peak response ratio of alcohol to methanol from the Sample solution
- \( R_{S} \) = peak response ratio of alcohol to methanol from the Standard solution
- \( C_{J} \) = concentration of dehydrated alcohol in the Standard solution (mg/mL)
- \( C_{S} \) = nominal concentration of alcohol in the Sample solution (mg/mL)

Average the percentage of alcohol found in the Transdermal Systems analyzed.
Acceptance criteria: 80%–120% of the labeled amount of C_{6}H_{12}O

PERFORMANCE TESTS

Change to read:

• DRUG RELEASE (724)
Test 1: For products labeled for dosing every 84 h
Medium: Water; 900 mL, deaerated
Apparatus 5: 50 rpm
Times: 24, 48, and 96 h
Mobile phase: Water and acetonitrile (3:2)
Standard solution: 9 µg/mL of USP Estradiol RS in dehydrated alcohol. Dilute this solution with Medium to obtain solutions having concentrations of about 0.9, 0.45, and 0.045 µg/mL.
Sample solution: At each sampling time interval, withdraw a 10-mL aliquot of the solution under test.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: Fluorimetric, with excitation at 220 nm and emission at 270 nm
Column: 4.6-mm × 3-cm; packing L1
Temperature: 40°
If the product complies with this test, the labeling

\[ \text{Test 2:} \]

\[
A_i = \text{Transdermal System label claim (mg)}
\]

\[
m = \text{slope of the calibration curve}
\]

\[
b = \text{y-intercept of the calibration curve}
\]

\[
L = \text{Transdermal System label claim (mg)}
\]

Tolerances: See Table 1.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (release rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>1.2%–6.0%</td>
</tr>
<tr>
<td>48</td>
<td>3.0%–11.4%</td>
</tr>
<tr>
<td>96</td>
<td>5.0%–16.3%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of estradiol \((\text{C}_{18}\text{H}_{22}\text{O}_{3})\) released at the times specified conform to \textit{Drug Release (724), Acceptance Table 1}.

\textbf{Test 2:} If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 2.

\textbf{Medium:} 0.005 M phosphate buffer, pH 5.5, containing 0.3% sodium lauryl sulfate; 500 mL

\textbf{Apparatus 5:} 100 rpm. Use a 76-mm stainless steel disk assembly. Adhere the patch to the disk assembly using transfer tape. [Note—A suitable tape is available as 3M adhesive transfer tape 927, www.mmm.com.]

\textbf{Times:} 1, 4, 8, and 24 h

\textbf{Mobile phase:} Acetonitrile and water (1:1)

\textbf{Standard stock solution:} 800 µg/mL of USP Estradiol RS in acetone

\textbf{Standard solution:} Dilute the \textit{Standard stock solution} with Medium to obtain a solution having a known concentration close to that expected in the solution under test, assuming 100% drug release.

\textbf{Sample solution:} At each sampling time interval, withdraw a known volume aliquot of the solution under test.

\textbf{Chromatographic system:} (See Chromatography (621), System Suitability.)

\textbf{Mode:} LC

\textbf{Detector:} UV 205 nm

\textbf{Column:} 3.9-mm × 30-cm; packing L1

\textbf{Flow rate:} 1.0 mL/min

\textbf{Injection size:} 100 µL

\textbf{System suitability:}

\textbf{Sample:} Standard solution

\textbf{Tailing factor:} NMT 2.0

\textbf{Relative standard deviation:} NMT 3.0%

\textbf{Analysis:} Calculate the amount of estradiol released at each sampling time:

\[
M_i = \text{amount of estradiol released into the Medium at a given sampling time (mg)}
\]

\[
r_i = \text{peak response from the Sample solution}
\]

\[
s_i = \text{peak response from the Standard solution}
\]

\[
C_i = \text{concentration of the Standard solution (mg/mL)}
\]

\[
V_i = \text{corrected volume of the Medium at a given sampling time (mL)}
\]

\[
m_r, m_{r2}, m_{r3} = \text{total amounts of estradiol released from the patch at given sampling times (mg)}
\]

\[
M_r, M_{r2}, M_{r3} = \text{amounts of estradiol released into the Medium at given sampling times (mg)}
\]

\[
V_o = \text{volume of the aliquot taken from the dissolution vessel at each sampling time (mL)}
\]

\[
V_i, V_{i2}, V_{i3} = \text{volumes of Medium at given sampling times (mL)}
\]

\[
L = \text{Transdermal System label claim (mg)}
\]

Tolerances: See Table 2.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (release rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15%–40%</td>
</tr>
<tr>
<td>4</td>
<td>45%–70%</td>
</tr>
<tr>
<td>8</td>
<td>70%–90%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of estradiol \((\text{C}_{18}\text{H}_{22}\text{O}_{3})\) released at the times specified confirm to \textit{Drug Release (724), Acceptance Table 1}.

\textbf{Test 3:} If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 3.

\textbf{Medium:} 1% (v/v) polysorbate 40 in water; 900 mL

\textbf{Apparatus 5:} 50 rpm

\textbf{Times:} 4, 8, and 24 h

\textbf{Standard stock solution:} Known concentration (mg/mL) of USP Estradiol RS in methanol

\textbf{Standard solution:} Five different concentrations within the range of the expected release amounts of estradiol, prepared as follows. Add 1.0 mL of polysorbate 40 into a 100-mL volumetric flask, and then add the required
amount of Standard stock solution. Mix well to dissolve the polysorbate 40, and dilute with water to volume.

Sample solution: At each sampling time interval, withdraw a known volume aliquot of the solution under test.

Mobile phase: Acetonitrile and water (2:3)

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm, 5-µm packing L1 for 9-cm² systems; 4.6-mm × 12.5-cm, 5-µm packing L1 for 18-, 27-, or 36-cm² systems. In any case, a guard column containing packing L1 is used.
Flow rate: 1.0 mL/min
Injection size: 50 µL

System suitability
Sample: Standard solution
Relative standard deviation: NMT 2.0%

Analysis: Calculate the cumulative release rate as a percentage of the labeled amount of estradiol:

Result = \[ \frac{[900(A - b)]/(1000 \times m \times l)}{L} \] × 100

where:
- \( A \) = peak area of estradiol in the Sample solution at each time interval
- \( b \) = y-intercept of the calibration curve
- \( m \) = slope of the calibration curve
- \( L \) = Transdermal System label claim (mg)

Tolerances: The percentages of the labeled amount of estradiol (C18H22O2) released at the times specified conform to Table 3, Table 4, and Table 5.

L1 (6 units)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (individual values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
</tr>
</tbody>
</table>

L2 (12 units)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (average of 12)</th>
<th>Amount Dissolved (individual values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
<td>34%–77%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
<td>50%–102%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
<td>NLT 68%</td>
</tr>
</tbody>
</table>

L3 (24 units)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (average of 24)</th>
<th>Amount Dissolved (individual for 22 units of 24)</th>
<th>Amount Dissolved (individual for 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
<td>34%–77%</td>
<td>29%–82%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
<td>50%–102%</td>
<td>43%–109%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
<td>NLT 68%</td>
<td>NLT 60%</td>
</tr>
</tbody>
</table>

Test 4: If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 4.

Table 3

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (individual values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (average of 12)</th>
<th>Amount Dissolved (individual values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
<td>34%–77%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
<td>50%–102%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
<td>NLT 68%</td>
</tr>
</tbody>
</table>

Table 5

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (average of 24)</th>
<th>Amount Dissolved (individual for 22 units of 24)</th>
<th>Amount Dissolved (individual for 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
<td>34%–77%</td>
<td>29%–82%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
<td>50%–102%</td>
<td>43%–109%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
<td>NLT 68%</td>
<td>NLT 60%</td>
</tr>
</tbody>
</table>

Table 6

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (release rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>20–40</td>
</tr>
</tbody>
</table>
If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 5.

### Apparatus 6:
50 rpm. Adhere the Transdermal System to the cylinder assembly using a strip of suitable double-sided transfer tape. Set cylinder height at 8 ± 2 mm above the vessel bottom.

### Medium:
Water, deaerated; 500 mL for 0.025 and 0.0375 mg/day dosage; 900 mL for 0.05, 0.075, and 0.1 mg/day dosage.

### Drug Release Test 5.
The percentages of the labeled amount of estradiol \( (C_{18}H_{22}O_2) \) released at the times specified conform to Dissolution (711), Acceptance Table 2.

#### Test 5:
If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 5.

##### Standard Solution
0.1 mg/mL of USP Estradiol RS

##### Standard Stock Solution
0.001 mg/mL of USP Estradiol RS

##### Sample Solution
At each sampling time interval, withdraw a known volume aliquot of the solution under test.

### Chromatographic System
(See Chromatography (621), System Suitability.)

#### Mode: LC

#### Detector: UV 225 nm

#### Column: 3.0-mm × 7.5-cm; 3.5-µm packing L1

#### Flow rate: 0.7 mL/min

#### Column temperature: 40°

#### Injection volume: 50 µL

#### Run time: NLT 1.5 times the retention time of estradiol

### System Suitability

#### Sample: Standard solution

#### Relative standard deviation: NMT 5.0%

#### Analysis

#### Samples: Standard solution and Sample solution

Calculate the concentration \( C_i \) of estradiol \( (C_{18}H_{22}O_2) \) in the sample withdrawn from the vessel at time point \( i \):

\[
C_i = \left( \frac{r_i}{r_s} \right) \times C_s
\]

#### Acceptance Table 2

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (release rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>48–68</td>
</tr>
<tr>
<td>12</td>
<td>70–90</td>
</tr>
</tbody>
</table>

#### Table 6 (continued)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (release rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>48–68</td>
</tr>
<tr>
<td>12</td>
<td>70–90</td>
</tr>
</tbody>
</table>

#### Table 7

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (individual values, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17–37</td>
</tr>
<tr>
<td>2</td>
<td>42–62</td>
</tr>
<tr>
<td>3</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

#### Table 6

The percentages of the labeled amount of estradiol \( (C_{18}H_{22}O_2) \) released at each time point \( i \):

\[
\text{Result}_i = \left( \frac{S_i}{L} \right) \times \left( \frac{1}{V} \right) \times 100
\]

\[
\text{Result}_2 = \left( \frac{S_2}{L} \right) \times \left( \frac{1}{(V - 2 \times V_0)} \right) \times 100
\]

\[
\text{Result}_3 = \left( \frac{S_3}{L} \right) \times \left( \frac{1}{(V - 2 \times V_0)} \right) \times 100
\]

### Uniformity of Dosage Units (905)
The results from the Transdermal Systems used in the Assay meet the requirements.

### Additional Requirements

#### Packaging and Storage:
Preserve in hermetic, light-resistant, unit-dose pouches.

#### Labeling:
The label states the total amount of estradiol in the Transdermal System and the release rate, in mg/day, for the duration of application of one system. When more than one Drug Release test is given, the labeling states the Drug Release test used only if Test 1 is not used.

#### USP Reference Standards

USP Estradiol RS

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