Minocycline Hydrochloride Extended-Release Tablets

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Posting Date                   30–Aug–2019
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Expert Committee               Chemical Medicines Monographs 1
Reason for Revision            Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Minocycline Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add Dissolution Tests 6 and 7 to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution tests.

- **Dissolution Test 6** was validated using an ACE C18 brand of L1 column. The typical retention time for minocycline is about 7.2 min.

The revision also necessitates a change in the table numbering in the test for Organic Impurities.

The Minocycline Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Praveen K. Pabba, Scientific Liaison (301-816-8540 or pkp@usp.org).
Minocycline Hydrochloride Extended-Release Tablets

**DEFINITION**
Minocycline Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of minocycline (C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>8</sub>·H<sub>2</sub>O).

**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.
- **B.** The UV absorption spectrum of the major peak of the Standard solution and that of the Standard solution exhibit maxima and minima at the same wavelengths, as obtained in the Assay.

**ASSAY**
- **PROCEDURE**
- Protect solutions containing minocycline from light.
- **Buffer:** 3.5 g/L of tetrabutylammonium hydrogen sulfate, 2 g/L of anhydrous citric acid, and 6.8 g/L of monobasic potassium phosphate. Adjust with 10 N sodium hydroxide to a pH of 7.0.
- **Mobile phase:** Acetonitrile and buffer (24:76).
- **Diluent:** Acetonitrile and water (20:80).
- **Standard solution:** 0.045 mg/mL of minocycline from USP Minocycline Hydrochloride RS in the Diluent. Store at 4° and use within 24 h.
- **Sample stock solution:** Nominally about 0.9 mg/mL of minocycline from Sample stock solution in Diluent. Centrifuge and use the clear supernatant. Store at 4° and use within 24 h.
- **Sample solution:** Nominally 0.045 mg/mL of minocycline from Sample stock solution in Diluent. Centrifuge and use the clear supernatant. Store at 4° and use within 24 h.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 277 nm. When this procedure is used for Identification test B, use a diode array detector set at 200–400 nm.
- **Column:** 4.6-mm × 15-cm; 5-µm packing L1.
- **Temperatures**
  - Column: 35°
  - Autosampler: 4°
- **Flow rate:** 1.3 mL/min
- **Injection volume:** 10 µL

**System suitability**
- **Sample:** Standard solution
- **Suitability requirements**
  - **Tailing factor:** NMT 1.5
  - **Relative standard deviation:** NMT 1.0%

**Analysis**
- **Samples:** Standard solution and Sample solution
- Calculate the percentage of the labeled amount of minocycline (C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>8</sub>·H<sub>2</sub>O) in the portion of Tablets taken:

  \[
  \text{Result} = \left( \frac{r_i}{r_o} \right) \times \left( \frac{C_i}{C_o} \right) \times P \times F \times 100
  \]

  \[
  C_o = \text{nominal concentration of minocycline in the Sample solution (mg/mL)}
  \]
  \[
  P = \text{potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)}
  \]
  \[
  F = \text{conversion factor, 0.001 mg/µg}
  \]

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

**PERFORMANCE TESTS**

Change to read:

- **Dissolution (711)**

  **Test 1**
  Protect solutions containing minocycline from light.
  **Medium:** pH 6.8 phosphate buffer; 900 mL
  **Apparatus 2:** 50 rpm
  **Times:** 1, 2, and 5 h
  **Standard stock solution:** 0.5 mg/mL of minocycline from USP Minocycline Hydrochloride RS in Medium
  **Standard solution:** (L/900) mg/mL of minocycline from Standard stock solution in Medium, where L is the label claim of minocycline in mg/Tablet
  **Sample solution:** Pass a portion of the solution under test through a suitable filter.

  **Instrumental conditions**
  Mode: UV
  **Analytical wavelength:** 348 nm
  **Cell:** See Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Tablet Strength (mg)</th>
<th>Cell Path Length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>0.5</td>
</tr>
<tr>
<td>90</td>
<td>0.2</td>
</tr>
<tr>
<td>135</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Blank:** Medium
**Analysis**
- **Samples:** Standard solution, Sample solution, and Blank
- Autozero the instrument using the Blank.
- Calculate the concentration (C) of minocycline (C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>8</sub>·H<sub>2</sub>O) in the sample withdrawn from the vessel at each time point (i):

  \[
  \text{Result} = \left( \frac{A_i}{A_s} \right) \times \frac{C_s}{C} \times P \times F
  \]

  \[
  A_i = \text{absorbance of the Sample solution at time point } i
  \]
  \[
  A_s = \text{absorbance of the Standard solution}
  \]
  \[
  C_s = \text{concentration of the Standard solution (mg/mL)}
  \]
  \[
  P = \text{potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)}
  \]
  \[
  F = \text{conversion factor, 0.001 mg/µg}
  \]

- Calculate the percentage of the labeled amount (Q) of minocycline (C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>8</sub>·H<sub>2</sub>O) dissolved at each time point (i):

  \[
  \text{Result}_i = C_s \times V \times (1/L) \times 100
  \]

  \[
  \text{Result}_1 = \left( \frac{(C_s \times V) - (C_s \times V_i)}{C_s \times V} \right) \times \frac{C_s}{C} \times P \times F \times 100
  \]

  \[
  \text{Result}_3 = \left( \frac{(C_s \times [V - (2 \times V_i)])}{C_s \times V} \right) \times \frac{C_s}{C} \times P \times F \times 100
  \]

  \[
  C_i = \text{concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)}
  \]
2 Minocycline

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2. Protect solutions containing minocycline from light.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Times: 1, 2, and 4 h

Standard solution: 0.0225 mg/mL of minocycline from USP Minocycline Hydrochloride RS in Medium

Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of Medium. Pass through a suitable filter. Dilute with Medium to a concentration that is similar to that of the Standard solution.

Instrumental conditions

Mode: UV

Analytical wavelength: 348 nm

Cell: 1 cm

Blank: Medium

Analysis

Samples: Standard solution and Sample solution

Autozero the instrument using the Blank.

Calculate the concentration \( C \) of minocycline \((C_{22}H_{22}N_{2}O_{3})\) in the sample withdrawn from the vessel at each time point \( i \):

\[
\text{Result} = \left( A_{i} / A_{o} \right) \times C_{s} \times D \times P \times F
\]

\( A_{i} \) = absorbance of the Sample solution at time point \( i \)

\( A_{o} \) = absorbance of the Standard solution

\( C_{s} \) = concentration of the Standard solution (mg/mL)

\( D \) = dilution factor (mL/mL)

\( P \) = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)

\( F \) = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount \( Q \) of minocycline \((C_{22}H_{22}N_{2}O_{3})\) dissolved at each time point \( i \):

\[
\text{Result}_{1} = C_{s} \times V \times (1/L) \times 100
\]

\[
\text{Result}_{2} = \left[ (C_{s} \times V) + (C_{i} \times V_{i}) \right] \times (1/L) \times 100
\]

\[
\text{Result}_{3} = \left[ (C_{s} \times V) + (C_{i} + C_{i} \times V_{i}) \right] \times (1/L) \times 100
\]

\( C_{i} \) = concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)

\( V \) = volume of Medium, 900 mL

\( L \) = label claim (mg/Tablet)

\( V_{s} \) = volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)

Tolerances: See Table 2.

Table 2

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20–45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>40–70</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amounts of minocycline \((C_{22}H_{22}N_{2}O_{3})\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3. Protect solutions containing minocycline from light.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Times: 0.5, 1.5, and 4 h

Standard solution: 0.021 mg/mL of minocycline from USP Minocycline Hydrochloride RS in Medium

Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of Medium. Pass through a suitable filter. Dilute with Medium to a concentration that is similar to that of the Standard solution.

Instrumental conditions

Mode: UV

Analytical wavelength: 265 nm

Cell: 1 cm

Blank: Medium

Analysis

Samples: Standard solution and Sample solution

Autozero the instrument using the Blank.

Calculate the concentration \( C \) of minocycline \((C_{22}H_{22}N_{2}O_{3})\) in the sample withdrawn from the vessel at each time point \( i \):

\[
\text{Result} = \left( A_{i} / A_{o} \right) \times C_{s} \times D \times P \times F
\]

\( A_{i} \) = absorbance of the Sample solution at time point \( i \)

\( A_{o} \) = absorbance of the Standard solution

\( C_{s} \) = concentration of the Standard solution (mg/mL)

\( D \) = dilution factor (mL/mL)

\( P \) = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)

\( F \) = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount \( Q \) of minocycline \((C_{22}H_{22}N_{2}O_{3})\) dissolved at each time point \( i \):

\[
\text{Result}_{1} = C_{s} \times V \times (1/L) \times 100
\]

\[
\text{Result}_{2} = \left[ (C_{s} \times V) + (C_{i} \times V_{i}) \right] \times (1/L) \times 100
\]

\[
\text{Result}_{3} = \left[ (C_{s} \times V) + (C_{i} + C_{i} \times V_{i}) \right] \times (1/L) \times 100
\]

\( C_{i} \) = concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)

\( V \) = volume of Medium, 900 mL

\( V_{s} \) = volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)

Tolerances: See Table 3.

Table 3

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>40–60</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>70–95</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amounts of minocycline \((C_{22}H_{22}N_{2}O_{3})\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.
If the product complies with this test, the labeling

1.5 mL/min

NLT 1.5 times the retention time of

(50 µL 1, 2, and 4 h 0.1 N hydrochloric acid; 900 mL 0.55 mg/mL of minocycline

100 rpm

LC

Standard solution

UV 280 nm

10°

At the times specified, withdraw 10

Dimethylformamide,

40°

Standard solution

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Test 4: If the product complies with this test, the labeling

V = label claim (mg/Tablet)

F = conversion factor, 0.001 mg/µg

P = potency of minocycline in USP Minocycline

D = dilution factor (mL/mL)

A = absorbance of the Sample solution at time point i

A = absorbance of the Standard solution

C = concentration of the Standard solution (mg/mL)

D = dilution factor (mL/mL)

P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)

F = conversion factor, 0.001 mg/µg

The percentages of the labeled amounts of minocycline (C21H23N2O5) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4. Protect solutions containing minocycline from light.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Times: 1, 2, and 4 h

Standard solution: (L/900) mg/mL of minocycline from USP Minocycline Hydrochloride RS in Medium, where L is the label claim of minocycline in mg/Tablet

Sample solution: At the times specified, withdraw 5 mL of the solution under test and replace with 5 mL of Medium. Pass through a suitable filter. Dilute with Medium to a concentration that is similar to that of the Standard solution.

Instrumental conditions

Mode: UV

Analytical wavelength: 353 nm

Cell: 1 cm

Blank: Medium

Analysis

Samples: Standard solution and Sample solution

Autozero the instrument using the Blank.

Calculate the concentration (C) of minocycline (C21H23N2O5) in the sample withdrawn from the vessel at each time point (i):

Result = (A - A) × C × D × P × F

A = absorbance of the Sample solution at time point i

A = absorbance of the Standard solution

C = concentration of the Standard solution (mg/mL)

D = dilution factor (mL/mL)

P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount (Q) of minocycline (C21H23N2O5) dissolved at each time point (i):

Result1 = C × V × (1/L) × 100

Result2 = [(C × V) + (C × V)] × (1/L) × 100

Result3 = [(C × V) + (C × V)] × (1/L) × 100

C = concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of Medium, 900 mL

The percentages of the labeled amounts of minocycline (C21H23N2O5) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 6: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 6. Protect solutions containing minocycline from light.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Times: 1, 2, and 4 h

Mobile phase: Dimethylformamide, tetrahydrofuran, 0.2 M ammonium oxalate solution, and 0.01 M edetate disodium solution (120:80:600:180). Adjust with ammonium hydroxide to a pH of 7.2.

Standard stock solution: 0.55 mg/mL of minocycline from USP Minocycline Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Minocycline Hydrochloride RS to a suitable volumetric flask, and dissolve with 70% of the flask volume of Medium and sonicate for 5 min. Dilute with Medium to volume.

Standard solution: (L/900) mg/mL of minocycline from Standard stock solution in Medium, where L is the label claim of minocycline in mg/Tablet

Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of Medium. Pass through a suitable filter and dilute with Medium to a concentration that is similar to that of the Standard solution.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Column: 40°C

Autosampler: 10°C

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: NLT 1.5 times the retention time of minocycline

System suitability

Sample: Standard solution

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the concentration (C) of minocycline (C21H23N2O5) in the sample withdrawn from the vessel at each time point (i):
4 Minocycline

**Change to read:**

**IMPURITIES**

**Organic impurities**

Protect solutions containing minocycline from light.

**Buffer, Mobile phase, and Diluent:** Prepare as directed in the Assay.

**Standard stock solution:** Use the Standard solution as directed in the Assay.

**Standard solution:** 0.009 mg/mL of minocycline from Standard stock solution in Diluent. Store at 4° and use within 24 h.

**Sample solution:** Use the Sample stock solution as directed in the Assay.

**Sensitivity solution:** 0.9 µg/mL of minocycline from Standard solution in Diluent. Store at 4° and use within 24 h.

**System suitability solution:** Heat a portion of the Standard stock solution at 60° for about 2 h and cool. This solution contains a mixture of 4-epiminocycline and minocycline. Store at 4° and use within 24 h.

**Chromatographic system:** Proceed as directed in the Assay, except use a flow rate of 1 mL/min.

**System suitability**

**Samples:** Standard solution, Sensitivity solution, and System suitability solution

**Suitability requirements**

**Resolution:** NLT 4.6 between minocycline and 4-epiminocycline, System suitability solution

**Tailing factor:** NMT 1.5, Standard solution

**Relative standard deviation:** NMT 2.0%, Standard solution

**Signal-to-noise ratio:** NLT 10, Sensitivity solution

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of each impurity in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_i}{r_o} \right) \times C_i \times P \times F \times \frac{1}{100}
\]

- **Result** = peak response of each impurity from the Sample solution
- **r_i** = peak response of each impurity from the Sample solution
- **r_o** = peak response of minocycline from the Standard solution
- **C_i** = concentration of USP Minocycline Hydrochloride RS (µg/mg)
- **C_o** = nominal concentration of minocycline in the Sample solution (mg/mL)

**Tolerances:** See Table 7.

**Table 7**

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45 mg/Tablet</td>
</tr>
<tr>
<td>2</td>
<td>55–75</td>
</tr>
<tr>
<td>3</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amounts of minocycline (C_{23}H_{22}N_{2}O_{5}) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Table 6**

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45 mg/Tablet</td>
</tr>
<tr>
<td>1</td>
<td>40–60</td>
</tr>
<tr>
<td>2</td>
<td>75–95</td>
</tr>
<tr>
<td>3</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of minocycline (C_{23}H_{22}N_{2}O_{5}) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 7:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 7.

Protect solutions containing minocycline from light.

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus:** 100 rpm

**Times:** 1, 2, and 4 h

**Standard stock solution:** 0.75 mg/mL of minocycline from USP Minocycline Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Minocycline Hydrochloride RS to a suitable volumetric flask, and dissolve with 50% of the flask volume of Medium and sonicate to dissolve. Dilute with Medium to volume.

**Standard solution:** 0.0015 mg/mL of minocycline in Medium from the Standard stock solution

**Sample solution:** At the times specified, withdraw 15 mL of the solution under test and replace with 15 mL of Medium. Pass through a suitable filter. Dilute with Medium to a concentration that is similar to that of the Standard solution.

**Instrumental conditions and Analysis:** Proceed as directed in Test 2.
P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)
\( F \) = conversion factor, 0.001 mg/µg

Acceptance criteria: See Table 8. The reporting threshold is 0.1%.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Epiminocycline (^a)</td>
<td>0.38</td>
<td>4.0</td>
</tr>
<tr>
<td>Desmethyl minocycline (^b), (^c)</td>
<td>0.46</td>
<td>—</td>
</tr>
<tr>
<td>Sancycline (^d)</td>
<td>0.68</td>
<td>—</td>
</tr>
<tr>
<td>Sa,6-Anhydrominocycline (^e)</td>
<td>0.81</td>
<td>—</td>
</tr>
<tr>
<td>Hydroxymethylminocycline (^f), (^l)</td>
<td>0.92</td>
<td>—</td>
</tr>
<tr>
<td>Minocycline</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total degradation products (^g)</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

\(^a\) (4R,4aS,5aR,12aS):4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrorotracene-2-carboxamide.

\(^b\) Process impurities are controlled in the drug substance and are not to be reported here. They are not included in total degradation products.

\(^c\) (4S,4aS,5aR,12aS)-4-Dimethylamino-3,10,12,12a-tetrahydroxy-7-methylamino-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrorotracene-2-carboxamide.

\(^d\) 6-Demethyl-6-deoxytetracycline; (4S,4aS,5aR,12aS)-4-Dimethylamino-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrorotracene-2-carboxamide.

\(^e\) (4S,4aS,12aS)-4,7-Bis(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12a-hexahydrorotracene-2-carboxamide.

\(^f\) (4S,4aS,5aR,12aS)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-N-(hydroxymethyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrorotracene-2-carboxamide.

\(^g\) Total degradation products does not include 4-epiminocycline.

ADDITIONAL REQUIREMENTS

• PACKAGING AND STORAGE: Store in tightly closed containers at controlled room temperature.

• LABELING: When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

• USP REFERENCE STANDARDS (11) USP Minocycline Hydrochloride RS