

**BRIEFING**

**Ribavirin Tablets.** A new USP Pending Monograph is proposed based on submitted data. The HPLC procedures in the Assay and in the tests for Dissolution and Organic Impurities are based on analyses performed using an Inertsil ODS-3V brand of L1 column. The typical retention time for ribavirin in the Assay and Dissolution tests is about 5.7 min. The typical retention time for ribavirin in the Organic Impurities test is about 9.4 min.

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C73295

**Add the following:**

**►Ribavirin Tablets**

Draft 1

**DEFINITION**

Ribavirin Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of ribavirin (C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub>).

**IDENTIFICATION**

- The retention time of the ribavirin peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

**ASSAY**

**PROCEDURE**

**Buffer:** 4.0 mg/mL of sodium dihydrogen phosphate dihydrate in water. Adjust with 5% sodium hydroxide solution to a pH of 5.0 ± 0.05. Pass the solution through a suitable 0.45-µm filter.

**Mobile phase:** Acetonitrile and *Buffer* (2:98)

**Diluent:** Acetonitrile and water (3:7)

**Standard stock solution:** 0.6 mg/mL of USP Ribavirin RS in *Diluent*

**Standard solution:** 0.03 mg/mL of USP Ribavirin RS in *Mobile phase* from the *Standard stock solution*

**Sample stock solution:** Transfer a portion of ribavirin equivalent to 1000 mg of ribavirin from finely powdered Tablets (NLT 10) to a 1000-mL volumetric flask. Add about 750 mL of *Diluent*, and sonicate with occasional shaking for 30 min. Cool to room temperature, dilute with *Diluent* to volume, and mix. Centrifuge and decant the supernatant.

**Sample solution:** 0.03 mg/mL of ribavirin in *Mobile phase* from *Sample stock solution*. Pass the solution through a suitable 0.45-µm filter.

**Chromatographic system**

(See *Chromatography* (621), *System Suitability*.)

**Mode:** LC

**Detector:** UV 207 nm

**Column:** 4.6-mm × 25-cm column; 5-µm packing L1

**Flow rate:** 1 mL/min

**Injection size:** 20 µL

**Run time:** 10 min

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Column efficiency:** NLT 2000 theoretical plates

**Tailing factor:** NLT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
Calculate the percentage of C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

$r_U$  = response of the ribavirin peak in the *Sample solution*

$r_S$  = response of the ribavirin peak in the *Standard solution*  
 $C_S$  = concentration of USP Ribavirin RS in the *Standard solution* (mg/mL)  
 $C_U$  = nominal concentration of ribavirin in the *Sample solution* (mg/mL)

**Acceptance criteria:** 95.0%–105.0%

**PERFORMANCE TESTS**

**DISSOLUTION (711)**

**Medium:** Water; 900 mL

**Apparatus 2:** 50 rpm

**Time:** 30 min

**Buffer and Mobile phase:** Proceed as directed in the Assay.

**Standard solution:** 0.22 mg/mL of USP Ribavirin RS in *Medium*

**Sample solution:** Pass the solution through a suitable 0.45-µm filter.

**Chromatographic system**

(See *Chromatography* (621), *System Suitability*.)

**Mode:** LC

**Detector:** UV 225 nm

**Column:** 4.6 mm × 25 cm; 5-µm packing L1

**Flow rate:** 1 mL/min

**Injection size:** 10 µL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Column efficiency:** NLT 2000 theoretical plates

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

Calculate the percentage of C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$r_U$  = peak response of ribavirin in the *Sample solution*  
 $r_S$  = peak response of ribavirin in the *Standard solution*  
 $C_S$  = concentration of USP Ribavirin RS in the *Standard solution* (mg/mL)  
 $L$  = tablet label claim (mg)  
 $V$  = volume of *Medium*, 900 mL

**Tolerances:** NLT 80% (Q) of the labeled amount of ribavirin is dissolved.

- UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

**IMPURITIES**

**Organic Impurities**

**PROCEDURE**

**Solution A:** 3.4 mg/mL of potassium dihydrogen phosphate in water. Adjust with 5% potassium hydroxide solution to a pH of 5.00 ± 0.05. Pass the solution through a suitable 0.45-µm filter.

**Solution B:** Acetonitrile

**Mobile phase:** See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
30	90	10
40	75	25
50	50	50
55	50	50
56	100	0
70	100	0

**Standard stock solution:** 0.4 mg/mL of USP Ribavirin RS in *Solution A*

**Standard solution:** 0.02 mg/mL of USP Ribavirin RS in *Solution A* from *Standard stock solution*

**Sample solution:** Transfer a portion of ribavirin equivalent to 100 mg of ribavirin from finely powdered Tablets (NLT 20) to a 200-mL volumetric flask. Add about 150 mL of *Solution A*, and sonicate with occasional shaking for 15 min. Cool to room temperature, dilute with *Solution A* to volume, and mix. Pass the solution through a suitable 0.45-µm filter.

2 / Ribavirin Tablets

**Chromatographic system**

(See *Chromatography* (621), *System Suitability*.)

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 25-cm column; 5-μm packing L1

**Flow rate:** 1 mL/min

**Injection size:** 20 μL

**Run time:** 70 min. [NOTE— Data collection is only for the first 55 min. The remaining gradient steps re-equilibrate the column.]

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 5.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

[NOTE— Known process impurities are listed in *Impurity Table 1*.]

Calculate the percentage of any unknown impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

$r_U$  = response of unknown impurity in the *Sample solution*

$r_S$  = response of ribavirin in the *Standard solution*

$C_S$  = concentration of USP Ribavirin RS in the *Standard solution* (mg/mL)

$C_U$  = nominal concentration of ribavirin in the *Sample solution* (mg/mL)

**Impurity Table 1**

Name	Relative Retention Time
Triazole acid <sup>a</sup>	0.35
Ribavirin acid <sup>b</sup>	0.40

[NOTE— These are process impurities listed for information only.]

<sup>a</sup> 1*H*-1,2,4-Triazole-3-carboxylic acid.

<sup>b</sup> 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylic acid.

<sup>c</sup> 1*H*-1,2,4-Triazole-3-carboxamide.

<sup>d</sup> 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

<sup>e</sup> Methyl 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylate.

<sup>f</sup> 1-(5-*O*-Acetyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide.

<sup>g</sup> 1-(5-*O*-Benzoyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide.

**Impurity Table 1** (Continued)

Name	Relative Retention Time
Triazole amide <sup>c</sup>	0.64
Ribavirin	1.0
Ribavirin 5-isomer <sup>d</sup>	1.37
Ribavirin methyl ester <sup>e</sup>	2.09
Ribavirin 5'-acetyl <sup>f</sup>	2.43
Ribavirin 5'-benzoyl <sup>g</sup>	4.83

[NOTE— These are process impurities listed for information only.]

<sup>a</sup> 1*H*-1,2,4-Triazole-3-carboxylic acid.

<sup>b</sup> 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylic acid.

<sup>c</sup> 1*H*-1,2,4-Triazole-3-carboxamide.

<sup>d</sup> 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

<sup>e</sup> Methyl 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylate.

<sup>f</sup> 1-(5-*O*-Acetyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide.

<sup>g</sup> 1-(5-*O*-Benzoyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide.

**Acceptance criteria**

**Individual unknown impurity:** NMT 0.10%. [NOTE— Disregard unknown peak area less than 0.05%.]

**Total impurities:** NMT 0.30%

**ADDITIONAL REQUIREMENTS**

• **PACKAGING AND STORAGE:** Preserve in tight containers. Store between 15° and 30°.

• **USP REFERENCE STANDARDS (11)**  
USP Ribavirin RS ◀ (1-Jan-2010)