

BRIEFING

Didanosine Tablets for Oral Suspension. A new USP Pending Monograph is proposed based on validated methods of analysis. The liquid chromatographic procedures in the *Assay* and the test for *Dissolution* are based on analyses performed with the Hypersil BDS C8 brand of L7 column. The typical retention time of didanosine in the *Assay* and the test for *Dissolution* is about 7 min. The HPLC procedure in the test for *Organic Impurities* is based on analyses performed with the Luna C18 brand of L1 column. The typical retention time of didanosine in the test for *Organic Impurities* is about 22 min.

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Add the following:

Didanosine Tablets for Oral Suspension

Draft 1

DEFINITION

Didanosine Tablets for Oral Suspension contain NLT 90.0% and NMT 110.0% of the labeled amount of didanosine ($C_{10}H_{12}N_4O_3$).

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

Buffer: 3.85 g/L of ammonium acetate in water. Adjust with 5% (v/v) acetic acid to a pH of 6.0.
Diluent: Acetonitrile and *Buffer* (25:75)
Mobile phase: Acetonitrile and *Buffer* (3:97)
Standard solution: 0.05 mg/mL of USP Didanosine RS in *Mobile phase*. [NOTE—Sonicate to dissolve if necessary.]
Sample stock solution: Nominally 0.25 mg/mL of didanosine in *Diluent* prepared as follows. Transfer didanosine from finely powdered Tablets (NLT 20) to a suitable size volumetric flask and add 50% of the final volume of *Diluent*. Sonicate the solution for 30 min, then shake for 10 min. Cool to room temperature, and dilute with *Diluent* to final volume. Centrifuge a portion of the resulting solution.
Sample solution: Nominally 0.05 mg/mL of didanosine in *Mobile phase* from the *Sample stock solution*. Pass a portion of the resulting solution through a suitable filter of 0.45- μ m pore size. Use within 24 h.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm \times 15-cm; 5- μ m packing L7
Flow rate: 1.5 mL/min
Injection volume: 20 μ L
Run time: 1.5 times the retention time of didanosine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of didanosine ($C_{10}H_{12}N_4O_3$) in the portion of Tablets taken:

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

- r_U = peak response of didanosine from the *Sample solution*
- r_S = peak response of didanosine from the *Standard solution*
- C_S = concentration of USP Didanosine RS in the *Standard solution* (mg/mL)
- C_U = nominal concentration of didanosine in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

DISSOLUTION (711)

Medium: Water; 900 mL
Apparatus 2: 75 rpm
Time: 45 min
Buffer, Mobile phase, and System suitability: Proceed as directed in the *Assay*.
Standard stock solution: 0.5 mg/mL of USP Didanosine RS in *Mobile phase*
Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of (L/1000) mg/mL, where L is the Tablet label claim, in mg.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size.
Chromatographic system: Proceed as directed in the *Assay*, except to use an injection volume of 10 μ L.

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of didanosine ($C_{10}H_{12}N_4O_3$) dissolved:

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

- r_U = peak response from the *Sample solution*
- r_S = peak response from the *Standard solution*
- C_S = concentration of USP Didanosine RS in the *Standard solution* (mg/mL)
- V = volume of *Medium*, 900 mL
- L = label claim (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of didanosine ($C_{10}H_{12}N_4O_3$) is dissolved.

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

IMPURITIES

ORGANIC IMPURITIES

Buffer: Proceed as directed in the *Assay*.
Solution A: Acetonitrile and *Buffer* (2:98)
Solution B: Acetonitrile
Mobile phase: See *Table 1*.

Table 1

| Time (min) | Solution A (%) | Solution B (%) |
|------------|----------------|----------------|
| 0.01 | 100 | 0 |
| 28 | 100 | 0 |
| 29 | 60 | 40 |
| 34 | 100 | 0 |
| 40 | 100 | 0 |

Diluent: Use *Solution A*.

Standard solution: 1 μ g/mL of USP Didanosine RS and 2.5 μ g/mL of USP Didanosine Related Compound A RS in *Diluent*. [NOTE—Sonicate to dissolve if necessary.]

Sample solution: Nominally 0.5 mg/mL of didanosine in *Diluent* prepared as follows. Transfer didanosine from finely powdered Tablets (NLT 20) to a suitable size volumetric flask, and add about 50% of the final volume of *Diluent*. Sonicate the solution for 30 min, then shake for about 10 min. Cool to room temperature, and dilute with *Diluent* to final volume. Pass a portion of the resulting solution through a suitable filter of 0.45- μ m pore size. [NOTE—Do not use after 24 h.]

Chromatographic system:

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

Mode: LC
 Detector: UV 254 nm
 Column: 4.6-mm × 15-cm; 5-µm packing L1
 Flow rate: 1.5 mL/min
 Injection volume: 20 µL
 Run time: 2 times the retention time of didanosine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*. [NOTE—Disregard any peaks less than 0.05%.]

Calculate the percentage of didanosine related compound A in the portion of Tablets taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

r_u = peak response of didanosine related compound A from the *Sample solution*

r_s = peak response of didanosine related compound A from the *Standard solution*

C_s = concentration of USP Didanosine Related Compound A RS in the *Standard solution* (mg/mL)

C_u = nominal concentration of didanosine in the *Sample solution* (mg/mL)

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

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

r_u = peak response of any unspecified impurity from the *Sample solution*

r_s = peak response of didanosine from the *Standard solution*

C_s = concentration of USP Didanosine RS in the *Standard solution* (mg/mL)

C_u = nominal concentration of didanosine in the *Sample solution* (mg/mL)

Acceptance criteria: See Table 2.

Table 2

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|-------------------------|------------------------------|
| Didanosine related compound A (Hypoxanthine) ^a | 0.13 | 0.50 |
| Inosine ^{b, h} | 0.30 | — |

^a 1H-Purin-6(9H)-one.

^b 9-β-D-Ribofuranosylhypoxanthine.

^c 9-(2'-Deoxy-β-D-ribofuranosyl)hypoxanthine.

^d 9-(2',3'-Anhydro-β-D-ribofuranosyl)hypoxanthine.

^e 9-(3'-Deoxy-β-D-ribofuranosyl)hypoxanthine.

^f 9-(2',3'-Dideoxy-2',3'-didehydro-β-D-ribofuranosyl)hypoxanthine.

^g 9-(2',3',5'-Trideoxy-β-D-ribofuranosyl)hypoxanthine.

^h Process impurity listed for information only.

Table 2 (Continued)

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|--|-------------------------|------------------------------|
| 2'-Deoxyinosine ^{c, h} | 0.37 | — |
| 2',3'-Anhydroinosine ^{d, h} | 0.44 | — |
| 3'-Deoxyinosine ^{e, h} | 0.46 | — |
| Dideoxydidehydroinosine ^{f, h} | 0.73 | — |
| Didanosine | 1.00 | — |
| 2',3',5'-Trideoxyinosine ^{g, h} | 1.42 | — |
| Any unspecified impurity | — | 0.10 |
| Total impurities | — | 1.0 |

^a 1H-Purin-6(9H)-one.

^b 9-β-D-Ribofuranosylhypoxanthine.

^c 9-(2'-Deoxy-β-D-ribofuranosyl)hypoxanthine.

^d 9-(2',3'-Anhydro-β-D-ribofuranosyl)hypoxanthine.

^e 9-(3'-Deoxy-β-D-ribofuranosyl)hypoxanthine.

^f 9-(2',3'-Dideoxy-2',3'-didehydro-β-D-ribofuranosyl)hypoxanthine.

^g 9-(2',3',5'-Trideoxy-β-D-ribofuranosyl)hypoxanthine.

^h Process impurity listed for information only.

SPECIFIC TESTS

• **LOSS ON DRYING (731)**

Sample: 4 powdered Tablets

Analysis: Dry the *Sample* at 130° for 16 h.

Acceptance criteria: NMT 6.0%

• **ACID-NEUTRALIZING CAPACITY (301)**

Sample: 200 mg

Acceptance criteria: NLT 15 mEq of acid is consumed.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

• **LABELING:** The label states that the Tablets are not to be swallowed whole, and that they may be chewed or dispersed in water before administration.

• **USP REFERENCE STANDARDS (11)**

USP Didanosine RS

USP Didanosine Related Compound A RS

Hypoxanthine or 1H-Purin-6(9H)-one.

C₅H₄N₄O 136.11 ◀ (1-Mar-2012)