Docetaxel

Type of Posting	Revision Bulletin
Posting Date	29–Jul–2016
Official Date	01–Aug–2016
Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Docetaxel monograph. The purpose for the revision is to add two specified impurities N-Formyl impurity and 6-Dichloroethoxycarbonyl Docetaxel in Table 2 in *Organic Impurities*, *Procedure 1*, to reflect the FDA-approved specifications.

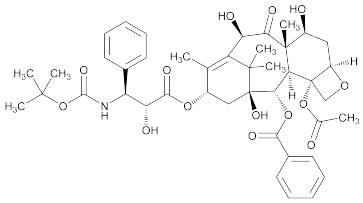
Additionally the following changes have been made based on the comments received:

- Add the Infrared Absorption <197A> in *Identification A* to provide the analysis options for more flexibility for the users
- Replace the acetic acid with glacial acetic acid in Diluent in *Assay* to be consistent with the validation
- Revise the resolution requirement in *Assay* and *Organic Impurities*, *Procedure 1* to be consistent with that in the Docetaxel Injection monograph for the similar procedure
- Revise the *Packaging and Storage* to include a flexible storage temperature

The Docetaxel Revision Bulletin supersedes the currently official Docetaxel monograph. The Revision Bulletin will be incorporated into *First Supplement to USP 40–NF 35*.

Should you have any questions, please contact Feiwen Mao (301–816–8320 or fm@usp.org).

Docetaxel



$C_{43}H_{53}NO_{14} \cdot 3H_2O$ 861.93

Anhydrous 807.88

Benzenepropanoic acid, β-[[(1,1-dimethylethoxy) carbonyl]amino]-α-hydroxy-, 12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester, [2a*R*-[2aα,4β,4aβ,6β,9α(α*R**,β*S**),11α,12α, 12aα,12bα]]-;
(2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

Trihydrate [148408-66-6].

Anhydrous [114977-28-5].

DEFINITION

Docetaxel contains NLT 97.5% and NMT 102.0% of docetaxel ($C_{43}H_{53}NO_{14}$), calculated on the anhydrous and solvent-free basis. [**CAUTION—**Docetaxel is cytotoxic. Great care should be taken to prevent inhaling particles of Docetaxel and exposing the skin to it.]

IDENTIFICATION

Change to read:

- **A. INFRARED ABSORPTION ⟨197⟩**
  [NOTE—Methods described in *Infrared Absorption* ⟨197K⟩, ⟨197M⟩, •⟨197A⟩,• (RB 1-Aug-2016) or ⟨197S⟩ may be used. Use a solution containing 60 mg/mL of Docetaxel in methylene chloride for ⟨197S⟩.]
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **PROCEDURE**
  Solution A: Water
  Solution B: Acetonitrile
  Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	72	28
9.0	72	28
39.0	28	72
39.1	72	28
50	72	28

Diluent: Acetonitrile, water, and •glacial• (RB 1-Aug-2016) acetic acid (100: 100: 0.1)
System suitability solution: 1 mg/mL of USP Docetaxel Identification RS in *Diluent*. [NOTE—USP Docetaxel Identification RS contains docetaxel and small amounts of 2-debenzoxyl 2-pentenoyl docetaxel, 6-oxodocetaxel, 4-epidocetaxel, and 4-epi-6-oxodocetaxel. See *Table 2*.]
Standard solution: 1.0 mg/mL of USP Docetaxel RS prepared as follows. Transfer a quantity of USP Docetaxel RS to a suitable volumetric flask, dissolve in alcohol equivalent to about 5% of the final volume, and dilute with *Diluent* to volume.
Sample solution: 1.0 mg/mL of Docetaxel prepared as follows. Transfer a quantity of Docetaxel to a suitable volumetric flask, dissolve in alcohol equivalent to about 5% of the final volume, and dilute with *Diluent* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 232 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L1
Temperatures
Autosampler: 10°
Column: 45°
Flow rate: 1.2 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT •3.5• (RB 1-Aug-2016) between 2-debenzoxyl 2-pentenoyl docetaxel and docetaxel, *System suitability solution*
Relative standard deviation: NMT 1.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of docetaxel ($C_{43}H_{53}NO_{14}$) in the portion of Docetaxel taken:

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

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

Acceptance criteria: 97.5%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%

Delete the following:

- **HEAVY METALS**
  Lead nitrate stock solution: Prepare as directed in *Heavy Metals* ⟨231⟩*, Special Reagents*.
  pH 3.5 acetate buffer: Prepare as directed in *Heavy Metals* ⟨231⟩*, Method I*.
  Diluent: Dimethylformamide and water (17:3)
  Standard lead solution: 1 µg/mL of lead in *Diluent* from the *Lead nitrate stock solution*, prepared on the day of use
  Test stock preparation: Dissolve 1 g of Docetaxel in 20 mL of *Diluent*.
  Test preparation: Place 12 mL of the *Test stock preparation* in a color-comparison tube, add 2 mL of *pH 3.5 acetate buffer* and 1.2 mL of thioacetamide–glycerin base TS, and mix.

Monitor preparation: Place 10 mL of the *Standard lead solution* in a color-comparison tube, add 2 mL of the *Test stock preparation*, and mix. Add 2 mL of *pH 3.5 acetate buffer* and 1.2 mL of thioacetamide–glycerin base TS, and mix.
Blank preparation: Place 10 mL of *Diluent* in a color-comparison tube, add 2 mL of the *Test stock preparation*, and mix. Add 2 mL of *pH 3.5 acetate buffer* and 1.2 mL of thioacetamide–glycerin base TS, and mix.
Analysis: Allow the *Test preparation*, *Monitor preparation*, and *Blank preparation* to stand for 2 min, and view downward over a white surface.
Acceptance criteria: Compared to the *Blank preparation*, the *Monitor preparation* shows a slight brown color. Any brown color in the *Test preparation* is not more intense than in the *Monitor preparation* (NMT 20 ppm).● (Official 1-Jan-2018)

Change to read:

- **ORGANIC IMPURITIES, PROCEDURE 1**

[NOTE—On the basis of the synthetic route, perform either *Procedure 1* or *Procedure 2*. *Procedure 1* is recommended if 10-deacetyl baccatin and 2-debenzoxyl 2-pentenoyl docetaxel are specified impurities. *Procedure 2* is recommended if O-BOC *N*-pyruvyl docetaxel is a specified impurity.]
System suitability solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Sensitivity solution: 0.5 µg/mL of USP Docetaxel RS in *Diluent* from the *Standard solution*
System suitability
Samples: *System suitability solution* and *Sensitivity solution*
Suitability requirements
Resolution: NLT ●3.5● (RB 1-Aug-2016) between 2-debenzoxyl 2-pentenoyl docetaxel and docetaxel, *System suitability solution*
Signal-to-noise ratio: NLT 10 for the docetaxel peak, *Sensitivity solution*
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Docetaxel taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*
r_T = sum of all peak responses from the *Sample solution*
F = relative response factor for each individual impurity (see *Table 2*)

Acceptance criteria: See *Table 2*. Disregard any peaks less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
10-Deacetyl baccatin (if present)[a,●b●] (RB 1-Aug-2016)	0.25	1.5	0.15
●*N*-Formyl impurity (if present)[b,c]	0.57	1.1	0.15● (RB 1-Aug-2016)
2-Debenzoxyl 2-pentenoyl docetaxel	0.97	0.63	0.5
Docetaxel	1.00	—	—
6-Oxodocetaxel	1.08	1.0	0.3
4-Epidocetaxel	1.13	1.0	0.3
4-Epi-6-oxodocetaxel	1.18	1.0	0.2
●6-Dichloroethoxy-carbonyl docetaxel (if present)[b,d]	1.31	0.82	0.15● (RB 1-Aug-2016)
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one 12b-acetate, 12-benzoate.
●[b] If possible from the manufacturing process.
[c] (2a*R*,4*R*,4a*S*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4, 9,11,12,12b-pentahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5,6-dione 12b-acetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-formyl-3-phenylisoserine.
[d] (2a*R*,4*R*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6-{[(2,2-Dichloroethoxy)carbonyl]oxy}-1,2a,3,4,4a,6,9,10,11,12,12a,12b-dodecahydro-4,9,11,12,12b-pentahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one 12b-acetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-tert-butoxycarbonyl-3-phenylisoserine.● (RB 1-Aug-2016)

- **ORGANIC IMPURITIES, PROCEDURE 2**

Solution A: Water
Solution B: Acetonitrile
Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	65	35
25	45	55
35	20	80
45	20	80
45.1	65	35
53	65	35

System suitability solution: 1 mg/mL of USP Docetaxel System Suitability Mixture RS in acetonitrile. [NOTE—USP Docetaxel System Suitability Mixture RS contains docetaxel and a small amount of 6-oxodocetaxel, O-BOC *N*-pyruvyl docetaxel, 4-epidocetaxel, and 4-epi-6-oxodocetaxel. See *Table 4*.]
Standard solution: 5.0 µg/mL of USP Docetaxel RS in acetonitrile
Sample solution: 1.0 mg/mL of Docetaxel in acetonitrile
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L1
Temperatures
Column: 40°
Sample: 4°
Flow rate: 1.2 mL/min
Injection volume: 10 µL
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 2.0 between O-BOC *N*-pyruvyl docetaxel and 4-epidocetaxel
Tailing factor: 0.8–1.5 for the docetaxel peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Docetaxel taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak area of each individual impurity from the *Sample solution*
r_S = peak area of docetaxel from the *Standard solution*
C_S = concentration of USP Docetaxel RS in the *Standard solution* (mg/mL)
C_U = concentration of Docetaxel in the *Sample solution* (mg/mL)
F = relative response factor for each individual impurity (see *Table 4*)

Acceptance criteria: See *Table 4*. Disregard any peaks less than 0.05%.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Docetaxel	1.0	—	—
6-Oxodocetaxel	1.19	1.1	0.15
O-BOC *N*-pyruvyl docetaxel[a]	1.24	0.80	0.15
4-Epidocetaxel	1.29	0.96	0.15
4-Epi-6-oxodocetaxel	1.42	1.2	0.15
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	2.0

[a] (2a*R*,4*R*,4a*S*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4, 9,11,12,12b-pentahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5,6-dione 12b-acetate, 12-benzoate, 9-ester with (2*R*,3*S*)-2-(*tert*-butoxycarbonyloxy)-3-(2-oxopropanamido)-3-phenylpropanoic acid.

SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS ⟨61⟩** and **TESTS FOR SPECIFIED MICROORGANISMS ⟨62⟩:** The total aerobic microbial limit does not exceed 10^2 cfu/g. The total molds and yeasts count does not exceed 10 cfu/g.
- **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** It contains NMT 0.4 USP Endotoxin Units/mg.
- **WATER DETERMINATION ⟨921⟩,** *Method I, Method Ic*: 5.0%–7.0%. If labeled as an anhydrous form: NMT 1.5%.
- **OPTICAL ROTATION ⟨781S⟩,** *Procedures, Specific Rotation*
Sample solution: 10 mg/mL in methanol
Acceptance criteria: −39° to −41° (t = 20°), calculated on the anhydrous and solvent-free basis. If labeled as an anhydrous form: −35° to −45° (t = 20°), calculated on the as-is basis.

ADDITIONAL REQUIREMENTS

- **LABELING:** Where it is an anhydrous form, the label so indicates. If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.

Change to read:

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers, and store at room temperature •or between 2° and 8°.• (RB 1-Aug-2016)
- **USP REFERENCE STANDARDS ⟨11⟩**
USP Docetaxel RS
USP Docetaxel Identification RS
It contains docetaxel and small amounts of the following:
2-Debenzoxyl 2-pentenoyl docetaxel: (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one 12b-acetate, 12-[(*E*)-2-methylbut-2-enoate], 9-ester with (2*R*,3*S*)-*N*-*tert*-butoxycarbonyl-3-phenylisoserine.
$C_{41}H_{55}NO_{14}$ 785.87
6-Oxodocetaxel: (2a*R*,4*S*,4a*S*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,9,11,12,12b-pentahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5,6-dione 12b-acetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-*tert*-butoxycarbonyl-3-phenylisoserine.
$C_{43}H_{51}NO_{14}$ 805.86
4-Epidocetaxel: (2a*R*,4*R*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one 12b-acetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-*tert*-butoxycarbonyl-3-phenylisoserine.
$C_{43}H_{53}NO_{14}$ 807.88
4-Epi-6-oxodocetaxel: (2a*R*,4*R*,4a*S*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4, 9,11,12,12b-pentahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5,6-dione 12b-acetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-*tert*-butoxycarbonyl-3-phenylisoserine.
$C_{43}H_{51}NO_{14}$ 805.86
USP Docetaxel System Suitability Mixture RS
Contains docetaxel and a small amount of 6-oxodocetaxel, O-BOC *N*-pyruvyl docetaxel, 4-epidocetaxel, and 4-epi-6-oxodocetaxel.
USP Endotoxin RS