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Fluconazole in Sodium Chloride Injection

(Title for this monograph—not to change until November 1, 2018)

(Prior to November 1, 2018, the current practice of labeling the article of commerce with the name Fluconazole Injection may be continued. Use of the name Fluconazole in Sodium Chloride Injection will be permitted as of May 1, 2016; however, the use of this name will not be mandatory until November 1, 2018. The 30-month extension will provide the time needed by manufacturers and users to make necessary changes.)

DEFINITION

Fluconazole in Sodium Chloride Injection is a sterile solution containing Fluconazole and Sodium Chloride. It contains NLT 90.0% and NMT 110.0% of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$).

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: 0.82 g/L of anhydrous sodium acetate in water. Adjust with 1 N acetic acid solution to a pH of 5.0.

Diluent: Methanol and *Buffer* (20:80)

Solution A: Methanol and *Buffer* (5:95)

Solution B: Acetonitrile and methanol (60:40)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
9	80	20
15	15	85
18	80	20
25	80	20

System suitability solution: 0.04 mg/mL each of benzyl alcohol and USP Fluconazole RS in *Diluent*

Standard solution: 0.2 mg/mL of USP Fluconazole RS in *Diluent*

Sample solution: Nominally 0.2 mg/mL of fluconazole from Injection in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 261 nm

Column: 4.0-mm × 10-cm; 3-µm packing L1

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

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

[NOTE—The relative retention times for benzyl alcohol and fluconazole are about 0.8 and 1.0, respectively, *System suitability solution*.]

Suitability requirements

Resolution: NLT 1.8 between benzyl alcohol and fluconazole, *System suitability solution*

Tailing factor: NMT 1.5 for the fluconazole peak, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) in the portion of Injection 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 the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

OTHER COMPONENTS

• **SODIUM CHLORIDE CONTENT**

Solution A: 2 g/L of polyvinyl alcohol in water

Solution B: Transfer 25 mL of 65% nitric acid to a 100-mL volumetric flask and dilute with water to volume.

Sample solution: Transfer 5 mL of Injection to a suitable container, and add 40 mL of water, 1 mL of *Solution A*, and 1 mL of *Solution B*.

Titrant: 0.1 N silver nitrate

Analysis: Perform potentiometric titration with *Titrant*. Each mL of *Titrant* is equivalent to 5.844 mg of sodium chloride (NaCl).

Acceptance criteria: 95%–105% of the labeled amount of sodium chloride (NaCl)

IMPURITIES

• **ORGANIC IMPURITIES, PROCEDURE 1: FOR NONPOLAR IMPURITIES**

[NOTE—On the basis of the synthetic route, perform either (a) *Procedure 1* and *Procedure 2*, or (b) *Procedure 3*, or (c) *Procedure 4*. *Procedure 3* is recommended if bistriazole ketone and epoxyfluconazole (see *Table 4*) are potential impurities. *Procedure 4* is recommended if fluconazole bromohydrine and epoxyfluconazole (see *Table 5*) are potential impurities.]

Buffer, Diluent, Solution A, and **Solution B:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	77	23
5	77	23
30	40	60
43	77	23
50	77	23

System suitability solution: 2.4 µg/mL of 1,4-benzoquinone and 20 µg/mL of USP Fluconazole RS in *Diluent*

Standard solution: 2 µg/mL of USP Fluconazole RS in *Diluent*

Sample solution: Nominally 1.0 mg/mL of fluconazole from Injection in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 261 nm

Column: 4.0-mm × 10-cm; 3-µm packing L1

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

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

[NOTE—The relative retention times for 1,4-benzoquinone and fluconazole are about 0.5 and 1.0, respectively, *System suitability solution*.]

Suitability requirements

Resolution: NLT 5.0 between 1,4-benzoquinone and fluconazole, *System suitability solution*

Tailing factor: NMT 1.5 for the fluconazole peak, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—For the following calculations, do not include peaks eluting before fluconazole and do not include impurities at relative retention times of 2.00–2.12 and 3.14–3.26. The disregarded impurities at the specified relative retention times are process impurities monitored in the drug substance. Furthermore, disregard any peak due to an excipient or any peak less than 0.02%. This test is for determination of the late-eluting peaks, and hence the early-eluting peaks are not quantitated using this procedure.]

Calculate the percentage of the largest unknown nonpolar impurity in the portion of Injection taken:

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

r_U = peak response of the largest unknown nonpolar impurity from the *Sample solution*

r_S = peak response of fluconazole from the *Standard solution*

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

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

Calculate the percentage of total unknown nonpolar impurities in the portion of Injection taken:

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

r_U = sum of the peak responses of all the unknown nonpolar impurities from the *Sample solution*

r_S = peak response of fluconazole from the *Standard solution*

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

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

Acceptance criteria

Largest unknown nonpolar impurity: NMT 0.1%

Total unknown nonpolar impurities: NMT 0.5%

- **ORGANIC IMPURITIES, PROCEDURE 2: FOR POLAR IMPURITIES**

Buffer, Diluent, Solution A, Solution B, Mobile phase, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 2 µg/mL of USP Fluconazole RS in *Diluent*

Sample solution: Nominally 0.2 mg/mL of fluconazole from Injection in *Diluent*

System suitability

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

[NOTE—The relative retention times for benzyl alcohol and fluconazole are about 0.8 and 1.0, respectively, *System suitability solution*.]

Suitability requirements

Resolution: NLT 1.8 between benzyl alcohol and fluconazole, *System suitability solution*

Tailing factor: NMT 1.5 for the fluconazole peak, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—The relative retention times of known related compounds are listed in *Table 3*.]

Calculate the percentage of the single largest unknown polar impurity in the portion of Injection taken:

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

r_U = peak response of the largest unknown polar impurity from the *Sample solution*

r_S = peak response of fluconazole from the *Standard solution*

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

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

Calculate percentage of the total unknown polar impurities in the portion of Injection taken:

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

r_U = sum of the peak responses of all the unknown polar impurities from the *Sample solution*

r_S = peak response of fluconazole from the *Standard solution*

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

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

Acceptance criteria: See *Table 3*. Disregard any peak due to an excipient or any peak less than 0.03%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Aminofluconazole quaternary salt[a]	0.30–0.36	—[b]
Fluconazole isomer[c]	0.47–0.59	—[b]
Fluconazole diol[d]	0.68–0.74	—[b]
Cyclohexanone[e]	0.77–0.83	—
Fluconazole	1.0	—
Largest unknown polar impurity	—	0.1
Total unknown polar impurities	—	0.5
Total unknown polar and nonpolar impurities (sum of results from *Procedure 1* and *Procedure 2*)	—	1.0

[a] 4-Amino-1-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)-4*H*-1,2,4-triazolium bromide.

[b] These are process impurities which are included in this table for identification only. These impurities are controlled in the drug substance. They are not to be reported for the drug product and are not included in the total impurities.

[c] 2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(4*H*-1,2,4-triazol-4-yl)propan-2-ol.

[d] 2-(2,4-Difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propane-1,2-diol.

[e] Potential impurity associated with drug product packaged in bags.

- **ORGANIC IMPURITIES, PROCEDURE 3**

Buffer: 0.63 g/L of ammonium formate in water

Mobile phase: Acetonitrile and *Buffer* (14:86)

Standard solution: 2 mg/mL of USP Fluconazole RS in *Buffer*. [Note—Use approximately 14% of the total volume of acetonitrile, and sonicate if necessary to facilitate dissolution.]

Sensitivity solution: 1 µg/mL of USP Fluconazole RS in *Mobile phase* from the *Standard solution*

Sample solution: Nominally 2 mg/mL of fluconazole in 0.9% aqueous solution of sodium chloride

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

[Note—The retention time for fluconazole is between 12 and 14 min.]

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2%, *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 Injection taken:

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

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of fluconazole from the *Standard solution*

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

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

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Bistriazole ketone[a]	0.13	0.2
Fluconazole isomer[b]	0.5	0.2
Fluconazole	1.0	—
Epoxyfluconazole[c]	2.6	0.2
Any other individual impurity	—	0.2
Total impurities	—	0.5

[a] 1,3-Bis(1*H*-1,2,4-triazol-1-yl)propan-2-one.

[b] 2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(4*H*-1,2,4-triazol-4-yl)propan-2-ol.

[c] 1-[2-(2,4-Difluorophenyl)-2,3-epoxypropyl]-1*H*-1-2,4-triazole.

• **Organic Impurities, Procedure 4**

Buffer: 13.4 g/L of dibasic sodium phosphate heptahydrate in water. Adjust with phosphoric acid to a pH of 7.0.

Mobile phase: Acetonitrile and *Buffer* (26:74)

Standard solution: 2 mg/mL of USP Fluconazole RS in *Mobile phase*

Sample solution: Nominally 2 mg/mL of fluconazole in 0.9% aqueous solution of sodium chloride

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 0.5 mL/min

Injection volume: 50 µL

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 each impurity in the portion of Injection taken:

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

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of fluconazole from the *Standard solution*

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

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

F = relative response factor (see *Table 5*)

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Aminofluconazole quaternary salt[a]	0.57	0.74	0.1
Fluconazole isomer[b]	0.68	0.93	0.1
Fluconazole diol[c]	0.91	1.3	0.1
Fluconazole	1.0	1.0	—
Fluconazole bromohydrine[d]	2.58	1.1	0.1
Epoxyfluconazole[e]	2.59	0.90	0.1
Any other individual impurity	—	1.0	0.1
Total impurities	—	—	0.5

[a] 4-Amino-1-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)-4*H*-1,2,4-triazol-1-ium bromide.

[b] 2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(4*H*-1,2,4-triazol-4-yl)propan-2-ol.

[c] 2-(2,4-Difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propane-1,2-diol.

[d] 1-Bromo-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

[e] 1-[2-(2,4-Difluorophenyl)-2,3-epoxypropyl]-1*H*-1-2,4-triazole.

SPECIFIC TESTS

- **Sterility Tests ⟨71⟩:** Meets the requirements
- **Bacterial Endotoxins Test ⟨85⟩:** NMT 0.416 USP Endotoxin Unit/mg of fluconazole
- **Other Requirements:** Meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Store at controlled room temperature.
- **Labeling:** If a test for *Organic Impurities* other than *Procedure 1* and *Procedure 2* is used, then the labeling states with which *Organic Impurities* test the article complies.
- **USP Reference Standards ⟨11⟩**
  USP Fluconazole RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
FLUCONAZOLE IN SODIUM CHLORIDE INJECTION	Documentary Standards Support	SM12020 Small Molecules 1

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