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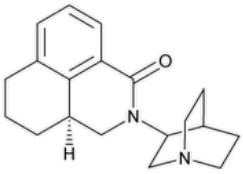
Palonosetron Hydrochloride



• HCl

$C_{19}H_{24}N_2O \cdot HCl$ 332.87

1*H*-Benzo[*de*]isoquinoline-1-one, 2,3,3a,4,5,6-hexahydro-2-[(3*S*)-1-azabicyclo[2.2.2]octan-3-yl],(*S*)-, hydrochloride;

(*S*)-2-[(3*S*)-Quinuclidin-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]isoquinolin-1-one hydrochloride CAS RN®: 135729-62-3; UNII: 23310D4I19.

DEFINITION

Palonosetron Hydrochloride contains NLT 98.0% and NMT 102.0% of palonosetron hydrochloride ($C_{19}H_{24}N_2O \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride*:** Meets the requirements

ASSAY

• **Procedure**

Mobile phase: Acetonitrile, water, and trifluoroacetic acid (280: 720: 0.67)

Standard stock solution: 0.7 mg/mL of USP Palonosetron Hydrochloride RS in methanol. Sonicate to dissolve, if necessary.

Standard solution: 0.014 mg/mL of USP Palonosetron Hydrochloride RS from the *Standard stock solution*, in *Mobile phase*

Sample stock solution: 0.7 mg/mL of Palonosetron Hydrochloride in methanol. Sonicate to dissolve, if necessary.

Sample solution: 0.014 mg/mL of Palonosetron Hydrochloride from the *Sample stock solution*, in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

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

Flow rate: 1 mL/min

Injection volume: 80 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of palonosetron hydrochloride ($C_{19}H_{24}N_2O \cdot HCl$) in the portion of Palonosetron Hydrochloride taken:

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

r_U = peak response of palonosetron from the *Sample solution*

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

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

C_U = concentration of Palonosetron Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Limit of Specified Impurities**

Mobile phase: *n*-Hexane, dehydrated alcohol, methanol, diethylamine, and trifluoroacetic acid (85: 7.5: 7.5: 0.2: 0.05)

System suitability stock solution 1: 0.05 mg/mL of each USP Palonosetron Related Compound B RS, USP Palonosetron Related Compound C RS, and USP Palonosetron Enantiomer RS in *Mobile phase*. Sonicate to dissolve, if necessary.

System suitability stock solution 2: 0.05 mg/mL USP Palonosetron Related Compound E RS in *Mobile phase*. Sonicate to dissolve, if necessary.

System suitability stock solution 3: 0.05 mg/mL USP Palonosetron Related Compound D RS in *Mobile phase*. Sonicate to dissolve, if necessary.

System suitability solution: 0.5 µg/mL each of USP Palonosetron Related Compound B RS, USP Palonosetron Related Compound C RS, and USP Palonosetron Enantiomer RS from *System suitability stock solution 1*; 2.5 µg/mL of USP Palonosetron Related Compound E RS from *System suitability stock solution 2*; 1.5 µg/mL of USP Palonosetron Related Compound D RS from *System suitability stock solution 3*; and 0.5 mg/mL of USP Palonosetron Hydrochloride RS in *Mobile phase*

Sensitivity solution: 0.25 µg/mL of USP Palonosetron Hydrochloride RS from *Standard solution*, in *Mobile phase*

Standard solution: 0.5 µg/mL of USP Palonosetron Hydrochloride RS in *Mobile phase*. Sonicate to dissolve, if necessary.

Sample solution: 500 µg/mL of Palonosetron Hydrochloride in *Mobile phase*. Sonicate to dissolve, if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; 5-µm packing L40

Temperatures

Autosampler: 10°

Column: 20°

Flow rate: 0.5 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of palonosetron

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.4 between palonosetron related compound C and palonosetron; NLT 2.5 between palonosetron and palonosetron related compound E, *System suitability solution*

Tailing factor: NLT 0.8 and NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *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 Palonosetron Hydrochloride 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 palonosetron from the *Standard solution*

C_S = concentration of USP Palonosetron Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = concentration of Palonosetron Hydrochloride in the *Sample solution* (µg/mL)

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Palonosetron enantiomer	0.85	1.0	0.1
Palonosetron related compound C	0.91	0.91	0.1
Palonosetron	1.00	—	—
Palonosetron related compound E	1.17	1.7	0.5
Palonosetron related compound B	1.64	1.1	0.1
Palonosetron related compound D	1.89	1.0	0.5

- **Limit of Palonosetron Related Compound A**

Buffer: 13 mL/L of 70% perchloric acid in water. Add 4 g of sodium hydroxide and adjust with dilute sodium hydroxide to a pH of 2.3.

Solution A: Acetonitrile and *Buffer* (20:80)

Solution B: Acetonitrile and *Buffer* (80:20)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
20	50	50
30	35	65
30.1	100	0
36	100	0

Diluent: Acetonitrile and water (50:50)

System suitability stock solution: 0.0225 mg/mL of USP Palonosetron Related Compound A RS in *Diluent*. Sonicate to dissolve, if necessary.

System suitability solution: 0.225 µg/mL of USP Palonosetron Related Compound A RS from *System suitability stock solution* and 0.15 mg/mL of USP Palonosetron Hydrochloride RS in *Diluent*. Sonicate to dissolve, if necessary.

Sensitivity solution: 0.075 µg/mL of USP Palonosetron Hydrochloride RS from *Standard solution* in *Diluent*

Standard solution: 0.15 µg/mL of USP Palonosetron Hydrochloride RS in *Diluent*. Sonicate to dissolve, if necessary.

Sample solution: 150 µg/mL of Palonosetron Hydrochloride in *Diluent*. Sonicate to dissolve, if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 3-µm packing L26

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The relative retention time for palonosetron related compound A is 1.05.]

Suitability requirements

Resolution: NLT 2.0 between palonosetron and palonosetron related compound A, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of palonosetron related compound A in the portion of Palonosetron Hydrochloride taken:

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

r_U = peak response of palonosetron related compound A from the *Sample solution*

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

C_S = concentration of USP Palonosetron Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = concentration of Palonosetron Hydrochloride in the *Sample solution* (µg/mL)

F = relative response factor, 0.94

Acceptance criteria: NMT 0.1%. The reporting threshold is 0.05%.

Change to read:

• **LIMIT OF UNSPECIFIED IMPURITIES**

Mobile phase▲, Standard stock solution,▲ (ERR 1-Jan-2023) and **Chromatographic system:** Proceed as directed in the *Assay*.

Peak identification stock solution: 0.07 mg/mL each of USP Palonosetron Related Compound A RS, USP Palonosetron Related Compound B RS, USP Palonosetron Related Compound D RS, and USP Palonosetron Related Compound E RS in methanol. Sonicate to dissolve, if necessary.

Peak identification solution: 0.07 µg/mL each of USP Palonosetron Related Compound A RS, USP Palonosetron Related Compound B RS, USP Palonosetron Related Compound D RS, and USP Palonosetron Related Compound E RS from the *Peak identification stock solution*, and 3.5 µg/mL of USP Palonosetron Hydrochloride RS from the *Standard stock solution*, in *Mobile phase*

Sensitivity solution: 0.0175 µg/mL of USP Palonosetron Hydrochloride RS in *Mobile phase*

Sample stock solution: 0.175 mg/mL of Palonosetron Hydrochloride in methanol. Sonicate to dissolve, if necessary.

Sample solution: 0.035 mg/mL of Palonosetron Hydrochloride from the *Sample stock solution*, in *Mobile phase*

System suitability

[NOTE—See *Table 3* for relative retention times.]

Sample: *Sensitivity solution*

Suitability requirements

Signal-to-noise ratio: NLT 10

Analysis

Sample: *Sample solution*

Calculate the percentage of each unspecified impurity in the portion of Palonosetron Hydrochloride taken:

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

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

r_T = sum of all peak responses from the *Sample solution*

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Palonosetron related compound E[a]	0.91	—
Palonosetron related compound D[a]	0.94	—
Palonosetron	1.0	—
Palonosetron related compound B[a]	1.1	—
Palonosetron related compound A[b]	1.2	—
Any individual unspecified impurity	—	0.1
Total impurities[c]	—	1.0

[a] These impurities are controlled in the test for *Limit of Specified Impurities* and are not to be reported here.

[b] This impurity is controlled in the test for *Limit of Palonosetron Related Compound A* and is not to be reported here.

[c] Total impurities include impurities controlled in the test for *Limit of Specified Impurities* and in the test for *Limit of Unspecified Impurities*.

SPECIFIC TESTS

• **pH** ⟨791⟩

Sample solution: 10 mg/mL in water

Acceptance criteria: 5.0–6.0

• **Loss on Drying** ⟨731⟩

Analysis: Dry under vacuum at 80° for 3 h.

Acceptance criteria: NMT 1.0%

• **Microbial Enumeration Tests** ⟨61⟩ and **Tests for Specified Microorganisms** ⟨62⟩**:** The total aerobic microbial count does not exceed 10^2 cfu/g, and the total combined molds and yeasts count does not exceed 10 cfu/g.

• **Bacterial Endotoxins Test** ⟨85⟩**:** Where the label states that Palonosetron Hydrochloride must be sterile or subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Palonosetron Hydrochloride is used can be met.

• **Sterility Tests** ⟨71⟩**:** Meets the requirements where the label states that Palonosetron Hydrochloride is sterile

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature, protected from light.

• **Labeling:** Where Palonosetron Hydrochloride must be sterile or subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled.

• **USP Reference Standards** ⟨11⟩

USP Palonosetron Enantiomer RS

(*R*)-2-[(3*R*)-Quinuclidin-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]isoquinolin-1-one hydrochloride.

$C_{19}H_{24}N_2O \cdot HCl$ 332.87

USP Palonosetron Hydrochloride RS

USP Palonosetron Related Compound A RS

Palonosetron *N*-oxide;

(*S*)-1-Oxo-2-[(3*S*)-quinuclidin-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]isoquinoline 1-oxide.

$C_{19}H_{24}N_2O_2$ 312.41

USP Palonosetron Related Compound B RS

Palonosetron-3-ene *N*-oxide;

(3*S*)-3-(1-Oxo-5,6-dihydro-1*H*-benzo[*de*]isoquinolin-2(4*H*)-yl)quinuclidine 1-oxide.

$C_{19}H_{22}N_2O_2$ 310.39

USP Palonosetron Related Compound C RS

Palonosetron *S,R*-diastereomer;

(*S*)-2-[(3*R*)-Quinuclidin-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]isoquinolin-1-one hydrochloride.

$C_{19}H_{24}N_2O \cdot HCl$ 332.87

USP Palonosetron Related Compound D RS

Palonosetron *R,S*-diastereomer or palonosetron 3a-epimer;
(*R*)-2-[(3*S*)-Quinuclidin-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]isoquinolin-1-one hydrochloride.
$C_{19}H_{24}N_2O \cdot HCl$ 332.87

USP Palonosetron Related Compound E RS

Palonosetron-3-ene;
2-[(3*S*)-Quinuclidin-3-yl]-2,4,5,6-tetrahydro-1*H*-benzo[*de*]isoquinolin-1-one hydrochloride.
$C_{19}H_{22}N_2O \cdot HCl$ 330.85

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

Topic/Question	Contact	Expert Committee
PALONOSETRON HYDROCHLORIDE	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 46(5)

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