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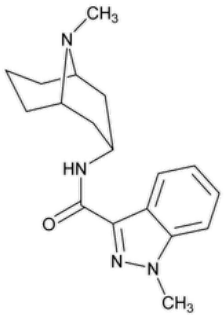
Granisetron Hydrochloride



• HCl

$C_{18}H_{24}N_4O \cdot HCl$ 348.87

1*H*-Indazole-3-carboxamide, 1-methyl-*N*-(9-methyl-9-azabicyclo[3.3.1]-non-3-yl)-, monohydrochloride, *endo*-;

1-Methyl-*N*-(9-methyl-*endo*-9-azabicyclo[3.3.1]non-3-yl)-1*H*-indazole-3-carboxamide monohydrochloride CAS RN®: 107007-99-8; UNII: 318F6L70J8.

DEFINITION

Granisetron Hydrochloride contains NLT 97.0% and NMT 102.0% of granisetron hydrochloride ($C_{18}H_{24}N_4O \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

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

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

ASSAY

• **Procedure**

Mobile phase: Acetonitrile, water, phosphoric acid, and hexylamine (200: 800: 1.6: 1.0). Adjust with triethylamine to a pH of 7.5 ± 0.05 (about 4 mL is needed). Make adjustments if necessary. (See *Chromatography ⟨621⟩, System Suitability*.)

Standard solution: 1.0 mg/mL of USP Granisetron Hydrochloride RS in *Mobile phase*

System suitability solution: Transfer 2 mL of *Standard solution* to a colorless glass vial, stopper it, and either expose the solution to sunlight for 4 h or place it under a UV lamp for 16 h (granisetron undergoes partial degradation to granisetron related compound C). A degradation of at least about 0.3% of granisetron to granisetron related compound C must be obtained as shown by the appearance of a corresponding peak in the chromatogram. If it is not obtained, again expose the solution to sunlight or place it under a UV lamp.

Sample solution: 1.0 mg/mL of Granisetron Hydrochloride in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 305 nm

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

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.5 between granisetron related compound C and granisetron, *System suitability solution*

Tailing factor: NMT 2.0 for the granisetron peak, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of granisetron hydrochloride ($C_{18}H_{24}N_4O \cdot HCl$) in the portion of Granisetron Hydrochloride taken:

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

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

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

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

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

Acceptance criteria: 97.0%–102.0% on the dried basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Organic Impurities**

[Note—Protect all solutions containing Granisetron Hydrochloride from light.]

Mobile phase, System suitability solution, and **Sample solution:** Prepare as directed in the *Assay*.

Peak identification solution: 0.01 mg/mL of USP Granisetron Related Compound A RS and 0.005 mg/mL of USP Granisetron Related Compound B RS in *Mobile phase*

Standard solution: 0.005 mg/mL of USP Granisetron Hydrochloride RS in *Mobile phase*

Chromatographic system: Proceed as directed in the *Assay*, except for the *Run time*.

Run time: NLT 2 times the retention time of granisetron

System suitability

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

Suitability requirements

Resolution: NLT 3.5 between granisetron related compound C and granisetron, *System suitability solution*

Tailing factor: NMT 2.0 for the granisetron peak, *System suitability solution*

Relative standard deviation: NMT 10%, *Standard solution*

Analysis

Samples: *Peak identification solution*, *Standard solution*, and *Sample solution*

Calculate the percentage of each impurity in the portion of Granisetron 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 granisetron from the *Standard solution*

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

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

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

Acceptance criteria: See *Table 1*. Discard any peaks observed in the blank. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Granisetron related compound D[a]	0.4	1.0	0.1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Granisetron related compound B	0.5	0.59	0.5
Granisetron related compound A	0.7	1.0	1.0
Granisetron related compound C[b]	0.8	1.0	0.2
Granisetron	1.0	–	–
Any other individual impurity	–	1.0	0.1
Total impurities	–	–	1.0

[a] 1-Methyl -1*H*-indazole-3-carboxylic acid.

[b] *N*-[(1*R*,3*r*,5S)-9-Azabicyclo[3.3.1]non-3-yl]-1-methyl-1*H*-indazole-3-carboxamide.

• **Limit of Granisetron Related Compound E**

Diluent: Acetonitrile and water (80:20)

Standard solution: 0.25 mg/mL of USP Granisetron Related Compound E RS in *Diluent*. [Note—USP Granisetron Related Compound E RS is the acetate salt of (1*R*,3*r*,5*S*)-9-Methyl-9-azabicyclo[3.3.1]nonan-3-amine. Use the correction factor stated on the label of the USP Reference Standard to calculate the concentration, as appropriate.]

Sample solution: 50 mg/mL of Granisetron Hydrochloride in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, General Procedures, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 2 µL

Developing solvent system: Ethyl acetate, isopropyl alcohol, and ammonium hydroxide (50: 30: 6.5)

Analysis

Samples: *Standard solution* and *Sample solution*

Proceed as directed in *Chromatography ⟨621⟩, General Procedures, Thin-Layer Chromatography* and develop the chromatogram until the solvent front has moved about half of the length of the plate. Dry the plate in air, and expose it to iodine vapor for 30 min.

Acceptance criteria: Any spot corresponding to granisetron related compound E from the *Sample solution* is not more intense than the corresponding spot from the *Standard solution* (0.5%).

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° for 4 h.

Acceptance criteria: NMT 0.5%

• **pH ⟨791⟩**

Sample solution: 10 mg/mL in carbon dioxide-free water

Acceptance criteria: 4.0–6.5

ADDITIONAL REQUIREMENTS

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

• **USP Reference Standards ⟨11⟩**

USP Granisetron Hydrochloride RS

USP Granisetron Related Compound A RS

2-Methyl-*N*-[(1*R*,3*r*,5*S*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-2*H*-indazole-3-carboxamide.

USP Granisetron Related Compound B RS

N-[(1*R*,3*r*,5*S*)-9-Methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide.

USP Granisetron Related Compound E RS

(1*R*,3*r*,5*S*)-9-Methyl-9-azabicyclo[3.3.1]nonan-3-amine, acetate salt.

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

Topic/Question	Contact	Expert Committee
GRANISETRON HYDROCHLORIDE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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