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Granisetron Hydrochloride Tablets

DEFINITION

Granisetron Hydrochloride Tablets contain an amount of Granisetron Hydrochloride equivalent to NLT 92.0% and NMT 108.0% of the labeled amount of granisetron ($C_{18}H_{24}N_4O$).

IDENTIFICATION

Delete the following:

▲• **A.** Thin-Layer Chromatographic Identification Test ⟨201⟩

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Developing solvent: Prepare a mixture of methylene chloride, alcohol, water, and ammonium hydroxide (60:40:5:2).

Standard solution: 0.44 mg/mL of USP Granisetron Hydrochloride RS in 0.1 N hydrochloric acid

Sample solution: Transfer a number of Tablets, equivalent to about 2 mg of granisetron, to a suitable container. Add 5.0 mL of 0.1 N hydrochloric acid, and sonicate for about 3 min. Pass through a 0.45-µm filter.

Application volume: 20 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Dry the spots under a current of warm air for about 5 min, and develop the plate in a paper-lined chromatographic chamber equilibrated with *Developing solvent*. Allow the chromatogram to develop until the solvent front has moved about 15 cm. Remove the plate, dry the plate under a cold air stream for about 10 min, and examine the plate under short-wavelength UV light.

Acceptance criteria: The principal spot from the *Sample solution* corresponds in appearance and R_F value to that of the *Standard solution*.▲ (USP 1-May-2021)

Add the following:

▲• **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

• **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**

▲[Note—Protect all solutions containing granisetron from light.]▲ (USP 1-May-2021)

Solution A: 15.6 g/L of sodium phosphate monobasic dihydrate in water. Adjust with phosphoric acid to a pH of 2.0, prior to final dilution.

Mobile phase: Methanol, tetrahydrofuran, and *Solution A* (24: 1.1: 75)

System suitability solution: 0.1 mg/mL of USP Granisetron Hydrochloride RS and 0.01 mg/mL each of USP Granisetron Related Compound B RS, USP Granisetron Related Compound C RS, and USP Granisetron Related Compound D RS in *Solution A*

Standard solution: 0.11 mg/mL of USP Granisetron Hydrochloride RS in *Solution A*

Sample solution: ▲Nominally▲ (USP 1-May-2021) 0.1 mg/mL of granisetron (base), based on the label claim, prepared as follows. Fill a suitable volumetric flask with *Solution A*, add 5 Tablets and sonicate for approximately 20 min until the Tablets disintegrate completely. Pass a portion of this solution through a membrane filter of 0.45-µm pore size, discarding the first few milliliters.

Chromatographic system

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

Mode: LC

Detector: UV 300 nm. ▲For *Identification A*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-May-2021)

Column: 4.6-mm × 15-cm; 4-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

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

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

Suitability requirements

▲▲ (USP 1-May-2021)

Resolution: NLT 2 between the granisetron and granisetron related compound C peaks, *System suitability solution*

Tailing factor: 0.8–1.5 for the granisetron peak, *System suitability solution*

Relative standard deviation: NMT 2.0% for 6 replicate injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of granisetron ($C_{18}H_{24}N_4O$) in each Tablet taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

M_{r1} = molecular weight of granisetron, 312.41

M_{r2} = molecular weight of granisetron hydrochloride, 348.87

Acceptance criteria: 92.0%–108.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Medium: pH 6.5 phosphate buffer (6.8 g/L of monobasic potassium phosphate in water; adjusted with 1 N sodium hydroxide to a pH of 6.5 prior to final dilution); 500 mL

Apparatus 2: 50 rpm

Time: 30 min

Solution A and **Mobile phase** ▲▲ (USP 1-May-2021) **:** Prepare as directed in the *Assay*.

Standard stock solution: Use *Standard solution* from the *Assay*.

Standard solution: 0.002 mg/mL of USP Granisetron Hydrochloride RS in *Solution A* from *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. If necessary, further dilute 5 mL of this solution with *Solution A* to (5 × *L*) mL, where *L* is the label claim in mg/Tablet.

Chromatographic system: Proceed as directed in the *Assay*, except for the *Injection volume*.

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–1.5

Relative standard deviation: NMT 2.0% for 6 replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of granisetron ($C_{18}H_{24}N_4O$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2}) \times V \times (1/L) \times D \times 100$$

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)

M_{r1} = molecular weight of granisetron, 312.41

M_{r2} = molecular weight of granisetron hydrochloride, 348.87

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

D = dilution factor for the *Sample solution*

Tolerances: NLT 75% (Q) of the labeled amount of granisetron ($C_{18}H_{24}N_4O$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

▲[Note—Protect all solutions containing granisetron from light.]▲ (USP 1-May-2021)

Solution A, Mobile phase, System suitability solution, Standard solution, Sample solution, and **System suitability:** Proceed as directed in the *Assay*.

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

Run time: NLT 3 times the retention time of the granisetron peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

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

M_{r1} = molecular weight of granisetron, 312.41

M_{r2} = molecular weight of granisetron hydrochloride, 348.87

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

Acceptance criteria: See *Table 1*. Reporting threshold is 0.1%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Granisetron related compound A[a,b]	0.5–0.6	—	—
Granisetron related compound B[c]	0.7	0.8	—
Granisetron	1.0	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Granisetron related compound C▲▲ (USP 1-May-2021)	1.2	1.0	0.7
Granisetron related compound D▲[c]▲ (USP 1-May-2021)	2.1–2.3	1.5	—
Any individual, unspecified impurity	—	—	0.5
Total specified impurities	—	—	1.3

[a] This is a process impurity and should not be included in the total specified impurities.

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

▲[c] To be included in total specified impurities▲ (USP 1-May-2021)

ADDITIONAL REQUIREMENTS

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

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Granisetron Hydrochloride RS

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.

▲$C_{17}H_{22}N_4O$ 298.39▲ (USP 1-May-2021)

USP Granisetron Related Compound C RS

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

▲$C_{17}H_{22}N_4O \cdot HCl$ 334.85▲ (USP 1-May-2021)

USP Granisetron Related Compound D RS

1-Methyl-1*H*-indazole-3-carboxylic acid.

▲$C_9H_8N_2O_2$ 176.18▲ (USP 1-May-2021)

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

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

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