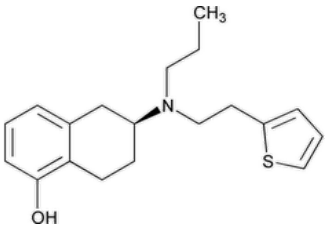
Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-Aug-2024
Document Type: USP Monographs
DocId: GUID-4A6F04CD-6206-43B4-845A-27AE30E7C8FE_5_en-US
DOI: https://doi.org/10.31003/USPNF_M8287_05_01
DOI Ref: n7774

Rotigotine

Change to read:



$C_{19}H_{25}NOS$ ▲315.48▲ (CN 1-Aug-2024)

1-Naphthalenol, 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino-(6*S*)-;

(-)-(*S*)-5,6,7,8-Tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol;

(6*S*)-6-[Propyl(2-(2-thienyl)ethyl)amino]-5,6,7,8-tetrahydro-1-naphthalenol CAS RN®: 99755-59-6.

DEFINITION

Rotigotine contains NLT 98.0% and NMT 102.0% of rotigotine ($C_{19}H_{25}NOS$).

IDENTIFICATION

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

Standard: USP Rotigotine RS

Acceptance criteria: Meets the requirements

• **B.** The retention time of the major peak of the *Identification solution* corresponds to the rotigotine–*S* isomer peak of the *System suitability solution*, as obtained in the *Limit of Rotigotine R-Enantiomer* test.

ASSAY

Change to read:

• **Procedure**

Solution A: 0.3 mL of trifluoroacetic acid in 1 L of water

Solution B: 0.2 mL of trifluoroacetic acid in 1 L of acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	82	18
2	82	18
24	50	50
24.1	82	18
27	82	18

Diluent A: 1 mL of trifluoroacetic acid in 1 L of water

Diluent B: 1 mL of trifluoroacetic acid in 1 L of acetonitrile

Standard stock solution: 1.3 mg/mL of USP Rotigotine Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Rotigotine Hydrochloride RS to a suitable volumetric flask. Add 5% of the flask volume of *Diluent B* and 40% of the flask volume of *Diluent A*. Sonicate to promote dissolution. [NOTE—A sonication time of NLT 20 min with shaking at 5-min intervals may be suitable.] Dilute with *Diluent A* to volume.

Standard solution: 650 µg/mL of USP Rotigotine Hydrochloride RS from *Standard stock solution* in *Diluent A*

System suitability solution: 0.005 mg/mL each of USP Rotigotine Related Compound G RS and USP Rotigotine Related Compound H RS in *Standard solution*

Sample solution: 600 µg/mL of Rotigotine in *Diluent A* prepared as follows. Transfer a suitable amount of Rotigotine to a suitable volumetric flask. Add 5% of the flask volume of *Diluent B* followed by 40% of the flask volume of *Diluent A*. Sonicate to promote dissolution. [NOTE—A sonication time of NLT 20 min with shaking at 5-min intervals may be suitable.]Dilute with *Diluent A* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.2 between rotigotine related compound G and rotigotine related compound H

Tailing factor: NMT 3.0 for rotigotine

Relative standard deviation: NMT 0.73% for rotigotine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of rotigotine ($C_{19}H_{25}NOS$) in the portion of Rotigotine taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

M_{r1} = molecular weight of rotigotine, ▲315.48▲ (CN 1-Aug-2024)

M_{r2} = molecular weight of rotigotine hydrochloride, 351.93

Acceptance criteria: 98.0%–102.0%

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%
- **LIMIT OF ROTIGOTINE *R*-ENANTIOMER**

Diluent A: Absolute alcohol, methanol, and 2-propanol (90:5:5)

Diluent B: 1 mL of diethylamine in 1 L of *Diluent A*

Mobile phase: Heptane, *Diluent A*, and diethylamine (98:2:0.1)

System suitability solution: 0.1 mg/mL of USP Rotigotine Racemate RS in *Diluent B*

Sample solution: 2 mg/mL of Rotigotine in *Diluent B*

Identification solution: 0.05 mg/mL of Rotigotine from the *Sample solution* in *Diluent B*

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 10-µm packing L40. [NOTE—A 4.6-mm × 5-cm guard column with L40 packing may be used.]

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: About 1.5 times the retention time of rotigotine

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for rotigotine *R*-isomer and rotigotine are 0.9 and 1.0, respectively. Use the chromatogram from the *Identification solution* for *Identification B*.]

Suitability requirements

Resolution: NLT 1.5 between rotigotine *R*-isomer and rotigotine

Tailing factor: NMT 2.0 for rotigotine

Analysis

Samples: *Sample solution* and *Identification solution*

Calculate the percentage of rotigotine *R*-isomer in the portion of Rotigotine taken:

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

r_U = peak response of rotigotine *R*-isomer from the *Sample solution*

r_T = sum of the peak responses of rotigotine *R*-isomer and rotigotine from the *Sample solution*

Acceptance criteria: NMT 0.15% of rotigotine *R*-isomer

Change to read:

• **ORGANIC IMPURITIES**

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

Standard solution: 0.65 µg/mL of USP Rotigotine Hydrochloride RS from *Standard stock solution* and *Diluent A*

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.2 between rotigotine related compound G and rotigotine related compound H, *System suitability solution*

Tailing factor: NMT 2.0 for rotigotine, *Standard solution*

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

Analysis

Samples: *Sample solution* and *Standard solution*

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

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

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

r_S = peak response from the *Standard solution*

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

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

M_{r1} = molecular weight of rotigotine, ▲315.48▲ (CN 1-Aug-2024)

M_{r2} = molecular weight of rotigotine hydrochloride, 351.93

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Desthienylethyl rotigotine[a]	0.2	0.30
Rotigotine related compound C[b]	0.6	0.30
Ethylrotigotine[c]	0.79	0.15
Rotigotine	1.0	—
Acetyl rotigotine[d]	1.46	0.15
Rotigotine related compound G	1.62	0.30
Rotigotine related compound H[e]	1.67	—
Rotigotine-*O*-tosylate[f]	2.42	0.15
Rotigotine-*O*-thienylethyl[g]	2.60	0.15
Any individual, unspecified impurity	—	0.10
Total impurities	—	1.0

[a] (*S*)-6-(Propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol.

[b] (*S*)-6-{[2-(Thiophen-2-yl)ethyl]amino}-5,6,7,8-tetrahydronaphthalen-1-ol.

[c] (*S*)-6-{Ethyl[2-(thiophen-2-yl)ethyl]amino}-5,6,7,8-tetrahydronaphthalen-1-ol.

[d] (6*S*)-6-[Propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-yl acetate.

[e] Included for *System suitability* evaluation only.

[f] (*S*)-6-{Propyl[2-(thiophen-2-yl)ethyl]amino}-5,6,7,8-tetrahydronaphthalen-1-yl 4-methylbenzenesulfonate.

[g] (*S*)-*N*-Propyl-5-[2-(thiophen-2-yl)ethoxy]-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine.

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I, Method Ia*:** NMT 0.2%

ADDITIONAL REQUIREMENTS

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

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Rotigotine RS

USP Rotigotine Hydrochloride RS

(6*S*)-6-[Propyl(2-(2-thienyl)ethyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol hydrochloride.

$C_{19}H_{25}NOS \cdot HCl$ 351.93

USP Rotigotine Related Compound G RS

(*S*)-6-{Bis[2-(thiophen-2-yl)ethyl]amino}-5,6,7,8-tetrahydronaphthalen-1-ol hydrochloride.

$C_{22}H_{25}NOS_2 \cdot HCl$ 420.03

USP Rotigotine Related Compound H RS

(*S*)-5-Methoxy-*N*-propyl-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine.

$C_{20}H_{27}NOS$ 329.50

USP Rotigotine Racemate RS

(*RS*)-6-{Propyl[2-(thiophen-2-yl)ethyl]amino}-5,6,7,8-tetrahydronaphthalen-1-ol.

$C_{19}H_{25}NOS$ ▲315.48▲ (CN 1-Aug-2024)

Topic/Question	Contact	Expert Committee
ROTIGOTINE	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 43(5)

Current DocID: GUID-4A6F04CD-6206-43B4-845A-27AE30E7C8FE_5_en-US
DOI: https://doi.org/10.31003/USPNF_M8287_05_01
DOI ref: n7774