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Add the following:

▲Prasugrel Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-prasugrel-tabs-20210528.

DEFINITION

Prasugrel Tablets contain an amount of prasugrel hydrochloride ($C_{20}H_{20}FNO_3S \cdot HCl$) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of prasugrel ($C_{20}H_{20}FNO_3S$).

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*.
- **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

Mobile phase: Acetonitrile and 0.1% phosphoric acid (30:70)

Diluent: Acetonitrile and water (50:50)

Standard stock solution: 0.55 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent* prepared as follows. Transfer an appropriate amount of USP Prasugrel Hydrochloride RS to a suitable volumetric flask. Add *Diluent* to about 70% of the volume of the flask and sonicate. Dilute with *Diluent* to volume.

Standard solution: 0.055 mg/mL of USP Prasugrel Hydrochloride RS from *Standard stock solution* in *Diluent*. Pass a portion of the solution through a suitable filter of 0.45-µm pore size and use the filtrate.

Sample stock solution: Nominally equivalent to 0.5 mg/mL of prasugrel prepared as follows. Transfer Tablets (NLT 10) to an appropriate volumetric flask, add *Diluent* to about 75% of the final volume of the flask, and sonicate with intermittent shaking to disperse the Tablets completely. Continue mixing with a suitable magnetic stirrer for 30 min. Dilute with *Diluent* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size and use the filtrate.

Sample solution: Nominally equivalent to 0.05 mg/mL of prasugrel from *Sample stock solution* in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

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

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 2.9 times the retention time of prasugrel

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 the labeled amount of prasugrel ($C_{20}H_{20}FNO_3S$) in the portion of Tablets taken:

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

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

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

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

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

M_{r1} = molecular weight of prasugrel, 373.44

M_{r2} = molecular weight of prasugrel hydrochloride, 409.90

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

▲**Test 1**▲ (RB 1-Aug-2021)

Solution A: 0.023 M citric acid prepared by dissolving 4.83 g of citric acid in 1000 mL of water

Solution B: 0.026 M dibasic sodium phosphate anhydrous prepared by dissolving 3.69 g of dibasic sodium phosphate anhydrous in 1000 mL of water

Medium: *Solution A* and *Solution B* (50:50). Adjust with *Solution A* or *Solution B* to a pH of 4.0; 900 mL

Apparatus 2: 75 rpm

Time: 20 min

Mobile phase: Acetonitrile and 0.1% phosphoric acid (30:70)

Standard stock solution: 0.3 mg/mL of USP Prasugrel Hydrochloride RS in acetonitrile. Sonicate to dissolve.

Standard solution

For Tablets labeled to contain 5 mg/Tablet: 0.003 mg/mL of USP Prasugrel Hydrochloride RS prepared as follows. Dilute 4 mL of *Standard stock solution* with *Medium* to 200 mL in a suitable container and mix. Immediately dilute 5 mL of this solution with acetonitrile to 10 mL. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

For Tablets labeled to contain 10 mg/Tablet: 0.006 mg/mL of USP Prasugrel Hydrochloride RS prepared as follows. Dilute 4 mL of *Standard stock solution* with *Medium* to 100 mL in a suitable container and mix. Immediately dilute 5 mL of this solution with acetonitrile to 10 mL. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Immediately dilute 5 mL of this solution with acetonitrile to 10 mL.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: NLT 2.6 times the retention time of prasugrel

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 the labeled amount of prasugrel ($C_{20}H_{20}FNO_3S$) dissolved:

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

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

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

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

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of prasugrel, 373.44

M_{r2} = molecular weight of prasugrel hydrochloride, 409.90

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of prasugrel ($C_{20}H_{20}FNO_3S$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: Citrate phosphate buffer pH 4.0 (Dissolve 4.63 g of dibasic sodium phosphate dihydrate and 4.83 g of citric acid in l000 mL of water. Adjust with 0.2 M dibasic sodium phosphate dihydrate or 0.1 M citric acid monohydrate to a pH of 4.0.); 900 mL

Apparatus 2: 75 rpm

Time: 30 min

Buffer A: Dissolve 1.36 g of monobasic potassium phosphate in 1000 mL of water. Adjust with 5% sodium hydroxide solution to a pH of 6.5.

Buffer B: Dissolve 1.36 g of monobasic potassium phosphate in 1000 mL of water. Adjust with 1% phosphoric acid to a pH of 4.0.

Mobile phase: Acetonitrile and *Buffer B* (85:15)

Diluent: Acetonitrile and *Buffer A* (50:50)

Standard stock solution: 0.25 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent*. Sonicate to dissolve.

Standard solution

For Tablets labeled to contain 5 mg/Tablet: 0.002 mg/mL of USP Prasugrel Hydrochloride RS prepared as follows. Dilute 5 mL of *Standard stock solution* with *Medium* to 200 mL. Dilute 5 mL of this solution with *Diluent* to 15 mL.

For Tablets labeled to contain 10 mg/Tablet: 0.004 mg/mL of USP Prasugrel Hydrochloride RS prepared as follows. Dilute 5 mL of *Standard stock solution* with *Medium* to 100 mL. Dilute 5 mL of this solution with *Diluent* to 15 mL.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard NLT 7 mL of filtrate. Immediately dilute 5 mL of this solution with *Diluent* to 15 mL.

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Autosampler: 7°

Column: 40°

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: NLT 1.5 times the retention time of prasugrel

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of prasugrel ($C_{20}H_{20}FNO_3S$) dissolved:

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

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

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

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

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of prasugrel, 373.44

M_{r2} = molecular weight of prasugrel hydrochloride, 409.90

D = dilution factor, 3

L = label claim (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of prasugrel ($C_{20}H_{20}FNO_3S$) is dissolved.▲ (RB 1-Aug-2021)

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

IMPURITIES

• **Organic Impurities, Procedure 1**

Solution A: 2.72 g of monobasic potassium phosphate in 1000 mL of 0.1% phosphoric acid

Solution B: Acetonitrile and methanol (90:10)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
15	75	25
30	75	25
40	60	40
65	20	80
75	20	80
76	90	10
85	90	10

Diluent: Acetonitrile and water (50:50)

Standard solution: 0.011 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent*. Sonication may be needed to dissolve.

Sensitivity solution: 0.5 µg/mL of USP Prasugrel Hydrochloride RS from *Standard solution* in *Diluent*

Sample solution: Nominally equivalent to 1 mg/mL of prasugrel prepared as follows. Transfer a portion of finely powdered Tablets (NLT 10), equivalent to 25 mg of prasugrel, to a 25-mL volumetric flask. Add 15 mL of *Diluent* and sonicate for 10 min with intermittent shaking while maintaining at 20°. Dilute with *Diluent* to volume and pass the solution through a suitable filter of 0.45-µm pore size. This solution should be prepared fresh and injected immediately.

Chromatographic system

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

Mode: LC

Detectors

For prasugrel: UV 220 nm

For prasugrel diketone: UV 252 nm

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

Column temperature: 35°

Flow rate: 1.6 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

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

Suitability requirements

Tailing factor: NMT 2.0 at 220 and 252 nm, *Standard solution*

Relative standard deviation: NMT 5.0% at 220 and 252 nm, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any specified or unspecified degradation products in the portion of Tablets taken:

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

r_U = peak response of each corresponding degradation product from the *Sample solution*

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

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

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

F = relative response factor (see *Table 2*)

M_{r1} = molecular weight of prasugrel, 373.44

M_{r2} = molecular weight of prasugrel hydrochloride, 409.90

Calculate the percentage of prasugrel diketone in the portion of Tablets taken (at 252 nm):

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

r_U = peak response of prasugrel diketone from the *Sample solution*

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

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

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

F = relative response factor (see *Table 2*)

M_{r1} = molecular weight of prasugrel, 373.44

M_{r2} = molecular weight of prasugrel hydrochloride, 409.90

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Thienotetrahydropyridinone [a,b]	0.07	—	—
Acetylthienotetrahydropyridine[b,c]	0.17	—	—
Prasugrel thiol analog[d]	0.62	1.0	0.33
Desacetyl hydroxyprasugrel[e]	0.88	1.64	0.40
Prasugrel	1.00	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desacetyl prasugrel diastereoisomer-1[f]	1.32	1.30	1.5
Desacetyl prasugrel diastereoisomer-2[f]	1.40	1.30	1.8
Prasugrel diketone[g]	1.55	2.00	0.40
Any unspecified degradation product	—	1.0	0.2
Total degradation products[h]	—	—	3.5

[a] 5,6,7,7a-Tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one.

[b] Both thienotetrahydropyridinone and acetylthienotetrahydropyridine are analyzed by *Organic Impurities, Procedure 2*.

[c] 4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate.

[d] (*Z*)-2-(1-(2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-4-mercaptopiperidin-3-ylidene) acetic acid.

[e] 5-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-7a-hydroxy-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one.

[f] 5-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one. Desacetyl prasugrel diastereoisomer-1 and desacetyl prasugrel diastereoisomer-2 are a pair of diastereomers.

[g] 1-Cyclopropyl-2-(2-fluorophenyl)ethane-1,2-dione.

[h] Include all impurities from *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 2*.

- **Organic Impurities, Procedure 2**

Solution A: Transfer 1.0 mL of perchloric acid (about 70%) to 1000 mL of water.

Solution B: Acetonitrile

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	94	6
6	94	6
12	35	65
14	20	80
15	10	90
16	10	90
16.1	94	6
22	94	6

Diluent: Acetonitrile and water (25:75)

Standard stock solution: 1.1 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent* prepared as follows. Transfer an appropriate amount of USP Prasugrel Hydrochloride RS to a suitable volumetric flask. Add *Diluent* to about 60% of the volume of the flask and sonicate. Dilute with *Diluent* to volume. Pass the solution through a suitable filter of 0.45-µm pore size.

Standard solution: 0.011 mg/mL of USP Prasugrel Hydrochloride RS from *Standard stock solution* in *Diluent*

Sample solution: Nominally equivalent to 1 mg/mL of prasugrel prepared as follows. Transfer a portion of finely powdered Tablets (NLT 10), equivalent to about 25 mg of prasugrel, to a 25-mL volumetric flask. Add 15 mL of *Diluent* and sonicate for 10 min with intermittent shaking while maintaining at 20°. Dilute with *Diluent* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L11

Column temperature: 20°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each specified degradation product in the portion of Tablets taken:

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

r_U = peak response of each specified degradation product from the *Sample solution*

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

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

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

F = relative response factor (see *Table 4*)

M_{r1} = molecular weight of prasugrel, 373.44

M_{r2} = molecular weight of prasugrel hydrochloride, 409.90

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Thienotetrahydropyridinone	0.27	1.59	0.3
Acetylthienotetrahydropyridine	0.79	0.71	0.3
Prasugrel	1.0	—	—

ADDITIONAL REQUIREMENTS

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

Add the following:

▲• **Labeling:** When more than one *Dissolution* test is given, the *Labeling* states the test used only if *Test 1* is not used.▲ (RB 1-Aug-2021)

• **USP Reference Standards ⟨11⟩**

USP Prasugrel Hydrochloride RS▲ (USP 1-Aug-2021)

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

Topic/Question	Contact	Expert Committee
PRASUGREL TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

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