Prasugrel Hydrochloride

Type of Posting	Revision Bulletin
Posting Date	28–Sep–2018
Official Date	01–Oct–2018
Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

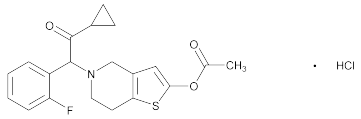
In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Prasugrel Hydrochloride monograph. The purpose of this revision is to widen the acceptance criteria for *Water Determination* <*921*> from NMT 0.2% to NMT 0.50% to be consistent with the FDA-approved drug products.

The Prasugrel Hydrochloride Revision Bulletin supersedes the Prasugrel Hydrochloride monograph which is becoming official in the *First Supplement to USP 41–NF 36*.

Should you have any questions, please contact Donald Min, Ph.D., Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@usp.org).

Add the following:

▲Prasugrel Hydrochloride



$C_{20}H_{20}FNO_3S \cdot HCl$ 409.90

Ethanone, 2-[2-(acetyloxy)-6,7-dihydrothieno[3,2-*c*] pyridin-5(4*H*)-yl]-1-cyclopropyl-2-(2-fluorophenyl)-, hydrochloride;

5-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride [389574-19-0].

DEFINITION

Prasugrel Hydrochloride contains NLT 97.0% and NMT 102.0% of prasugrel hydrochloride ($C_{20}H_{20}FNO_3S \cdot HCl$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨197⟩**:** [Note—Methods described in ⟨197K⟩ or ⟨197A⟩ may be used.]
- **B.** The retention time of the prasugrel 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**

Buffer: 10 mM monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.8.
Mobile phase: Acetonitrile and *Buffer* (35:65)
Diluent: Acetonitrile and water (70:30)
Standard solution: 0.1 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent*
Sample solution: 0.1 mg/mL of Prasugrel Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 260 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 2.5 times the retention time of prasugrel
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0%
Relative standard deviation: NMT 1.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of prasugrel hydrochloride ($C_{20}H_{20}FNO_3S \cdot HCl$) in the portion of Prasugrel Hydrochloride taken:

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

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

Acceptance criteria: 97.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **Residue on Ignition** ⟨281⟩**:** NMT 0.2%
- **Organic Impurities, Procedure 1**

Buffer: 10 mM monobasic potassium phosphate in water
Mobile phase: Acetonitrile, tetrahydrofuran, and *Buffer* (10:25:65)
Diluent: Acetonitrile and water (70:30)
Solution A: 150 µL of piperidine in 50 mL of acetonitrile
System suitability stock solution: 0.1 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent* prepared as follows. Transfer 5 mg of USP Prasugrel Hydrochloride RS to a 50-mL volumetric flask. Add 20 mL of *Diluent* and mix to dissolve. Add 1 mL of *Solution A* and dilute with *Diluent* to volume. Heat the solution at 50° for 1 h and cool to room temperature.
System suitability solution: 0.02 mg/mL of USP Prasugrel Hydrochloride RS from the *System suitability stock solution* in *Diluent*
Standard solution: 0.015 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent*
Sensitivity solution: 0.3 µg/mL of USP Prasugrel Hydrochloride RS from the *Standard solution* in *Diluent*
Sample solution: 1.5 mg/mL of Prasugrel Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 15-cm; 3-µm packing L1
Temperatures
Autosampler: 10°
Column: 40°
Flow rate: 0.9 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of prasugrel
System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
[Note—See *Table 1* for the relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between desacetyl prasugrel diastereomer 1 and desacetyl prasugrel diastereomer 2 peaks, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each specified process impurity in the portion of Prasugrel Hydrochloride taken:

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

r_U = peak response of each specified impurity 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 = concentration of Prasugrel Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Desacetyl prasugrel diastereomer 1[a]	0.43	—
Desacetyl prasugrel diastereomer 2[a]	0.45	—
Desfluoro prasugrel[b]	0.9	0.20
Prasugrel	1.0	—
4-Fluoro prasugrel[c]	1.2	0.15
3-Fluoro prasugrel[d]	1.3	0.30

[a] 5-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one. Desacetyl prasugrel diastereomer 1 and desacetyl prasugrel diastereomer 2 are a pair of diastereomers. They are used for resolution measurement only.
[b] 5-(2-Cyclopropyl-2-oxo-1-phenylethyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate.
[c] 5-[2-Cyclopropyl-1-(4-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate.
[d] 5-[2-Cyclopropyl-1-(3-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate.

• **ORGANIC IMPURITIES, PROCEDURE 2**

Buffer: 25 mM monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 4.0.
Solution A: Acetonitrile and *Buffer* (10:90)
Solution B: Acetonitrile and water (90:10)
Solution C: 150 µL of piperidine in 50 mL of acetonitrile
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
2	100	0
30	0	100
37	0	100
38	100	0
45	100	0

Diluent: Acetonitrile and water (70:30)
System suitability solution: 0.1 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent* prepared as follows. Transfer 5 mg of USP Prasugrel Hydrochloride RS to a 50-mL volumetric flask. Add 20 mL of *Diluent* and mix to dissolve. Add 1 mL of *Solution C* and dilute with *Diluent* to volume. Heat the solution at 50° for 1 h and cool to room temperature.
Standard solution: 0.1 mg/mL of USP Prasugrel Hydrochloride RS in *Diluent*
Sensitivity solution: 2 µg/mL of USP Prasugrel Hydrochloride RS from the *Standard solution* in *Diluent*
Sample solution: 10 mg/mL of Prasugrel Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 15-cm; 4-µm packing L87
Column temperature: 45°
Flow rate: 1.5 mL/min
Injection volume: 5 µL
System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
[NOTE—See *Table 3* for the relative retention times.]
Suitability requirements
Resolution: NLT 0.9 between the desacetyl prasugrel diastereomer 1 and desacetyl prasugrel diastereomer 2 peaks, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each specified and unspecified degradation product in the portion of Prasugrel Hydrochloride taken:

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

r_U = peak response of each 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 = concentration of Prasugrel Hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desacetyl hydroxyprasugrel[a]	0.74	1.0	0.15
Prasugrel diketone[b]	0.78	1.0	0.20
Desacetyl prasugrel diastereomer 1[c]	0.86	1.0	0.20
Desacetyl prasugrel diastereomer 2[c]	0.87	1.0	0.50
Prasugrel	1.0	—	—
Prasugrel chlorobutyryl analog[d]	1.06	0.73	0.30
Any individual unspecified degradation product	—	1.0	0.10
Total degradation products	—	—	1.0

[a] 5-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-7a-hydroxy-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one.
[b] 1-Cyclopropyl-2-(2-fluorophenyl)ethane-1,2-dione.
[c] 5-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one. Desacetyl prasugrel diastereomer 1 and desacetyl prasugrel diastereomer 2 are a pair of diastereomers.
[d] 5-[5-Chloro-1-(2-fluorophenyl)-2-oxopentyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate.

SPECIFIC TESTS

Change to read:

• **WATER DETERMINATION** ⟨921⟩**,** *Method I, Method Ic***:** NMT ▲0.50%▲ (RB 1-Oct-2018)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature.

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Prasugrel Hydrochloride RS
  ▲ 1S (USP41)