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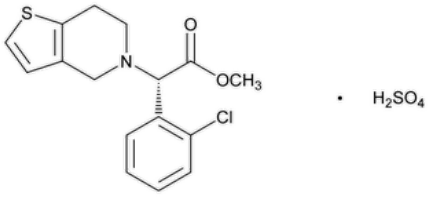
Clopidogrel Bisulfate



$C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ 419.90

Thieno[3,2-*c*]pyridine-5(4*H*)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (*S*)-, sulfate (1:1);

Methyl (+)-(*S*)-α-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate, sulfate (1:1) CAS RN®: 120202-66-6; UNII: 08I79HTP27.

DEFINITION

Clopidogrel Bisulfate contains NLT 97.0% and NMT 101.5% of clopidogrel bisulfate ($C_{16}H_{16}ClNO_2S \cdot H_2SO_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **C.** **Identification Tests—General, *Sulfate*⟨191⟩:** Meets the requirements

ASSAY

• **Procedure**

[Note—For all clopidogrel related compounds, the concentrations are expressed as bisulfate salts. Use bisulfate salt equivalents stated on USP Reference Standards labels to calculate the concentrations as appropriate.]

Buffer: 1.36 g/L of monobasic potassium phosphate in water

Mobile phase: Acetonitrile and *Buffer* (25:75)

System suitability stock solution: 100 µg/mL of USP Clopidogrel Bisulfate RS and 200 µg/mL of USP Clopidogrel Related Compound B RS in methanol

System suitability solution: 2.5 µg/mL of USP Clopidogrel Bisulfate RS and 5.0 µg/mL of USP Clopidogrel Related Compound B RS in *Mobile phase* from *System suitability stock solution*

Standard stock solution: 1.0 mg/mL of USP Clopidogrel Bisulfate RS in methanol

Standard solution: 0.1 mg/mL in *Mobile phase* from the *Standard stock solution*

Sample stock solution: 1 mg/mL of Clopidogrel Bisulfate in methanol

Sample solution: 0.1 mg/mL in *Mobile phase*, from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; packing L57

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

[Note—The relative retention times for the two enantiomers of clopidogrel related compound B and for clopidogrel are 0.8, 1.2, and 1.0, respectively.]

Suitability requirements

Resolution: Greater than 2.5 between clopidogrel and the first enantiomer of clopidogrel related compound B, *System suitability solution*

Relative standard deviation: NMT 1.0% from clopidogrel bisulfate, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of clopidogrel bisulfate ($C_{16}H_{16}ClNO_2S \cdot H_2SO_4$) in the portion of the sample taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

C_U = concentration of *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–101.5% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities**

[Note—For all clopidogrel related compounds, the concentrations are expressed as bisulfate salts. Use bisulfate salt equivalents stated on USP Reference Standards labels to calculate the concentrations as appropriate.]

Buffer: 0.96 g/L sodium 1-pentanesulfonate. Adjust with phosphoric acid to a pH of 2.5.

Solution A: Acetonitrile

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Buffer (%)	Solution A (%)	Solution B (%)
0	85	10	5
3	85	10	5
48	30	65	5
68	30	65	5

Diluent: Acetonitrile and *Buffer* (60:40)

System suitability solution: 6.5 mg/mL of USP Clopidogrel Bisulfate RS and 0.01 mg/mL each of USP Clopidogrel Related Compound A RS and USP Clopidogrel Related Compound B RS in *Diluent*

Standard solution: 6.5 µg/mL of USP Clopidogrel Bisulfate RS in *Diluent*

Sample solution: 6.5 mg/mL of Clopidogrel Bisulfate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for clopidogrel related compound A, clopidogrel, and clopidogrel related compound B are given in *Table 2*.]

Suitability requirements

Peak-to-valley ratio (H_P /H_V): NLT 10 where H_p is the height above the baseline of the peak due to clopidogrel related compound B and H_V is the height above the baseline of the lowest point of the curve separating clopidogrel related compound B and clopidogrel, *System suitability solution*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of clopidogrel related compound A, clopidogrel related compound B, and any other individual impurity in the portion of the sample taken:

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

r_U = peak response of clopidogrel related compound A, clopidogrel related compound B, or any other impurity from the *Sample solution*

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

C_S = concentration of the *Standard solution* (mg/mL)

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Clopidogrel related compound A[a]	0.4	0.2
Clopidogrel	1.0	—
Clopidogrel related compound B[b]	1.1	0.3
Any other impurity[c]	—	0.10
Total impurities	—	0.5

[a] (+)-(*S*)-(*o*-Chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetic acid.

[b] Methyl (+/−)-(*o*-chlorophenyl)-4,5-dihydrothieno[2,3-*c*]pyridine-6(7*H*)-acetate.

[c] Disregard any peak less than 0.05%.

- **Limit of Clopidogrel Related Compound C**

Mobile phase: Heptane and dehydrated alcohol (85:15)

Standard solution: 0.02 mg/mL each of USP Clopidogrel Bisulfate RS, USP Clopidogrel Related Compound B RS, and USP Clopidogrel Related Compound C RS prepared as follows. Dissolve a quantity of USP Clopidogrel Bisulfate RS, USP Clopidogrel Related Compound B RS, and USP Clopidogrel Related Compound C RS in dehydrated alcohol (about 50% of the volume of the flask), and dilute with heptane to volume.

Sample solution: 2 mg/mL of Clopidogrel Bisulfate prepared as follows. Transfer 100 mg of Clopidogrel Bisulfate to a 50-mL volumetric flask, dissolve in 25 mL of dehydrated alcohol, and dilute with heptane to volume.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 10-µm packing L80

Flow rate: 0.8 mL/min

Injection volume: 10 µL

Run time: 1.25 times the retention time of clopidogrel

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for clopidogrel related compound B, clopidogrel, and clopidogrel related compound C are 0.7, 1.0, and 0.6, respectively.]

Suitability requirements

Resolution: NLT 2.0 between clopidogrel related compound C and clopidogrel related compound B

Signal-to-noise ratio: NLT 20 for clopidogrel related compound C peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of clopidogrel related compound C in the portion of the sample taken:

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

r_U = peak response of clopidogrel related compound C from *Sample solution*

r_S = peak response of clopidogrel related compound C from *Standard solution*

C_S = concentration of the clopidogrel related compound C in *Standard solution* (mg/mL)

C_U = concentration of Clopidogrel Bisulfate in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.5%

SPECIFIC TESTS

• **LOSS ON DRYING ⟨731⟩**

Analysis: Dry a sample at 105° for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers and store at controlled room temperature.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Clopidogrel Bisulfate RS

USP Clopidogrel Related Compound A RS

(+)-(*S*)-(*o*-Chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetic acid, hydrochloride.

$C_{15}H_{14}ClNO_2S \cdot HCl$ 344.26

USP Clopidogrel Related Compound B RS

Methyl (+/−)-(*o*-chlorophenyl)-4,5-dihydrothieno[2,3-c]pyridine-6(7*H*)-acetate, hydrochloride.

$C_{16}H_{17}Cl_2NO_2S$ 358.28

USP Clopidogrel Related Compound C RS

Methyl (−)-(*R*)-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate, hydrogen sulfate.

$C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ 419.90

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

Topic/Question	Contact	Expert Committee
CLOPIDOGREL BISULFATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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