Loperamide Hydrochloride

Type of Posting	Revision Bulletin
Posting Date	29–May–2020
Official Date	01–Nov–2020
Expert Committee	Chemical Medicines Monographs 3

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Loperamide Hydrochloride monograph. The purpose for the revision is to address the inadvertent omission of text that was published in the *Pharmacopeial Forum* (*PF*) and approved by the Expert Committee. Specifically, a revision for *Organic Impurities* was proposed in *PF 43(4)*, and ultimately was approved by the Expert Committee; however, total impurities was inadvertently omitted from *Table 2* when the monograph was published as final approved text in the *USP-NF*.

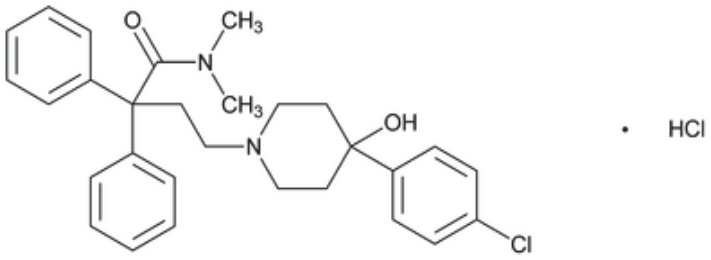
In addition, the cross-reference to *Chromatography <621>* has been corrected from “Chromatography <621>, General Procedures, Thin-Layer Chromatography” to “Chromatography <621>, System Suitability” under *Chromatographic system* in the test for *Organic Impurities*.

The Loperamide Hydrochloride Revision Bulletin supersedes the currently official Loperamide Hydrochloride monograph.

Should you have any questions, please contact Andrea F. Carney**,** Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8155 or afc@usp.org).

Revision Bulletin
Official: November 1, 2020

Loperamide Hydrochloride



Click image to enlarge

$C_{29}H_{33}ClN_2O_2 \cdot HCl$ 513.50
1-Piperidinebutanamide, 4-(4-chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-, monohydrochloride;
4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide hydrochloride [34552-83-5].

DEFINITION

Loperamide Hydrochloride contains NLT 98.0% and NMT 102.0% of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K
- **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride***

Sample solution: Dissolve about 30 mg of Loperamide Hydrochloride in 0.5 mL of methanol. Add 1.5 mL of water and 1 mL of 6 N ammonium hydroxide. A precipitate forms. Centrifuge, decant, and acidify the supernatant with diluted nitric acid.

Acceptance criteria: Meets the requirements

ASSAY

Change to read:

- **Procedure**

▲**Sample solution:** Dissolve 400 mg of Loperamide Hydrochloride in 50 mL of alcohol and add 5.0 mL of 0.01 N hydrochloric acid.

Analysis: Titrate the *Sample solution* with 0.1 N sodium hydroxide VS (see *Titrimetry ⟨541⟩*), determining the endpoint potentiometrically. Read the volume of 0.1 N sodium hydroxide added between the two points of inflection. Each milliliter of 0.1 N sodium hydroxide is equivalent to 51.35 mg of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$).▲ (USP 1-May-2020)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

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

Change to read:

- **Organic Impurities**

▲**Solution A:** 17.0 g/L of tetrabutylammonium hydrogen sulfate in water

Solution B: Acetonitrile

Mobile phase: See *Table 1*. Return to original conditions and re-equilibrate the system.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10

Time (min)	Solution A (%)	Solution B (%)
15	30	70
17	30	70

System suitability solution: 10 mg/mL of USP Loperamide System Suitability Mixture RS in methanol. See *Table 2* for the relative retention times of the main components of the mixture.

Standard solution: 20 µg/mL of USP Loperamide Hydrochloride RS in methanol

Sensitivity solution: 5 µg/mL of USP Loperamide Hydrochloride RS in methanol, from the *Standard solution*

Sample solution: 10 mg/mL of Loperamide Hydrochloride in methanol

Chromatographic system

(See *Chromatography ⟨621⟩*, ▲*System Suitability*▲ (RB 1-Nov-2020).)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Peak-to-valley ratio: NLT 1.5 for loperamide *cis-N*-oxide and anhydroloperamide; NLT 1.5 for loperamide piperidinolamide and loperamide biphenyl analog, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Loperamide Hydrochloride taken:

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

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

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

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

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Chlorophenylpiperidinol	0.2	1.0	0.2
Deschloroloperamide	0.8	0.59	0.2
Loperamide	1.0	—	—
Loperamide *trans-N*-oxide	1.1	1.0	0.2
Loperamide *cis-N*-oxide	1.16	1.0	0.2
Anhydroloperamide	1.18	1.0	0.2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Loperamide piperidinolamide	1.3	1.0	0.2
Loperamide biphenyl analog	1.4	0.77	0.2
Loperamide quaternary salt	1.7	1.0	0.2
Any other individual impurity	—	1.0	0.10▲ (USP 1-May-2020)
▲Total impurities	—	—	0.3▲ (RB 1-Nov-2020)

SPECIFIC TESTS

- **Loss on Drying** ⟨731⟩

  Analysis: Dry at 105° for 4 h.

  Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.

Change to read:

- **USP Reference Standards** ⟨11⟩

  USP Loperamide Hydrochloride RS

  ▲ USP Loperamide System Suitability Mixture RS

The mixture contains loperamide hydrochloride and the following impurities (other impurities may also be present):

Chlorophenylpiperidinol;
4-(4-Chlorophenyl)piperidin-4-ol. $C_{11}H_{14}ClNO$ 211.69

Deschloroloperamide;
4-(4-Hydroxy-4-phenylpiperidin-1-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide. $C_{29}H_{34}N_2O_2$ 442.59

Loperamide *trans*-*N*-oxide;
(1*r*,4*s*)-4-(4-Chlorophenyl)-1-[4-(dimethylamino)-4-oxo-3,3-diphenylbutyl]-4-hydroxypiperidine 1-oxide. $C_{29}H_{33}ClN_2O_3$ 493.04

Loperamide *cis*-*N*-oxide;
(1*s*,4*r*)-4-(4-Chlorophenyl)-1-[4-(dimethylamino)-4-oxo-3,3-diphenylbutyl]-4-hydroxypiperidine 1-oxide. $C_{29}H_{33}ClN_2O_3$ 493.04

Anhydroloperamide;
4-[4-(4-Chlorophenyl)-5,6-dihydropyridin-1(2*H*)-yl]-*N,N*-dimethyl-2,2-diphenylbutanamide. $C_{29}H_{31}ClN_2O$ 459.02

Loperamide piperidinolamide;
1,4-Bis[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-2,2-diphenylbutan-1-one. $C_{38}H_{40}Cl_2N_2O_3$ 643.64

Loperamide biphenyl analog;
4-[4-(4′-Chlorobiphenyl-4-yl)-4-hydroxypiperidin-1-yl]-*N,N*-dimethyl-2,2-diphenylbutanamide. $C_{35}H_{37}ClN_2O_2$ 553.13

Loperamide quaternary salt;
4-(4-Chlorophenyl)-1,1-bis[4-(dimethylamino)-4-oxo-3,3-diphenylbutyl]-4-hydroxypiperidin-1-ium chloride. $C_{47}H_{53}Cl_2N_3O_3$ 778.85▲ (USP 1-May-2020)

Page Information:

Not Applicable

DocID: