Diphenoxylate Hydrochloride

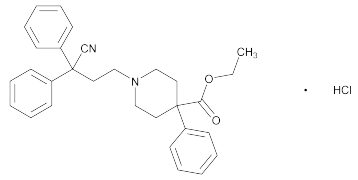
Type of Posting	Revision Bulletin
Posting Date	29–Jan–2016
Official Date	01–Feb–2016
Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Diphenoxylate Hydrochloride monograph. The purpose for the revision is to widen the limit for diphenoxylic acid impurity from NMT 0.15% to NMT 0.50%, to reflect the FDA-approved specifications.

The Diphenoxylate Hydrochloride Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into *Second Supplement* to *USP 39–NF 34*.

Should you have any questions, please contact Elena Gonikberg, Ph.D, Principal Scientific Liaison (301–816-8251 or eg@usp.org.)

Diphenoxylate Hydrochloride



$C_{30}H_{32}N_2O_2 \cdot HCl$ 489.05

4-Piperidinecarboxylic acid, 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl-, ethyl ester, monohydrochloride;

Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate monohydrochloride [3810-80-8].

DEFINITION

Diphenoxylate Hydrochloride contains NLT 98.0% and NMT 102.0% of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩**
- **B. IDENTIFICATION TESTS—GENERAL ⟨191⟩,** *Chloride*: A saturated solution meets the requirements.

ASSAY

- **PROCEDURE**

Sample: 400 mg of Diphenoxylate Hydrochloride

Analysis: Dissolve the *Sample* in 40 mL of alcohol and add 5.0 mL of 0.01 N hydrochloric acid. Titrate with 0.1 N alcoholic sodium hydroxide VS (see *Titrimetry* ⟨541⟩), determining the endpoint potentiometrically. Read the volume of 0.1 N alcoholic sodium hydroxide added between the two points of inflection. Each mL of 0.1 N alcoholic sodium hydroxide is equivalent to 48.91 mg of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$).

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

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Solution A: Adjust 900 mL of water with phosphoric acid to a pH of 2.3, and dilute with water to 1000 mL.

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	75	25
5	75	25
40	15	85

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

System suitability solution: 1.0 mg/mL of USP Diphenoxylate Hydrochloride RS and 0.005 mg/mL of USP Diphenoxylate Related Compound A RS in *Diluent*. Sonicate for about 2 min to dissolve.

Standard solution: 1.0 µg/mL of USP Diphenoxylate Hydrochloride RS in *Diluent*

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

Sample solution: 1.0 mg/mL of Diphenoxylate Hydrochloride in *Diluent*. Sonicate for about 2 min to dissolve.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 2.0 mL/min
Injection volume: 20 µL

System suitability
Samples: *System suitability solution* and *Sensitivity solution*
Suitability requirements
Resolution: NLT 5.0 between diphenoxylate related compound A and diphenoxylate, *System suitability 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 Diphenoxylate Hydrochloride taken:

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

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of diphenoxylate from the *Standard solution*
C_S = concentration of USP Diphenoxylate Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Diphenoxylate Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*. Disregard any peak below 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Diphenoxylic acid (diphenoxylate related compound A)	0.8	●0.50● (RB 1-Feb-2016)
Diphenoxylate	1.0	—
Any other individual impurity	—	0.10
Total impurities	—	0.5

SPECIFIC TESTS

- **LOSS ON DRYING ⟨731⟩**

Analysis: Dry at 105° for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light. Store at room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Diphenoxylate Hydrochloride RS
USP Diphenoxylate Related Compound A RS
Diphenoxylic acid;
1-(3-Cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid.
$C_{28}H_{28}N_2O_2$ 424.53