mixer to effect dissolution. Dilute with *Solution A* to volume, and mix. Filter, and use the filtrate as the *Test solution* immediately, or refrigerate and use within 24 hours.

Procedure—Proceed as directed for *Procedure* in the test for *Related compounds* under *Loracarbef*, except to omit the injection of the *Phenylglycine solution*. Calculate the percentage of each related compound in the Suspension taken by the formula:

$$100(C/Y)(r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Loracarbef RS in the *Standard solution; Y* is the concentration, in mg per mL, of loracarbef in the *Test solution;* r_i is the response of any related compound obtained from the *Test solution;* and r_S is the loracarbef response obtained from the *Standard solution:* not more than 1.0% of any individual related compound is found, and the sum of all related compounds is not more than 4.0%.

Assay—

Mobile phase, Standard preparation, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay* under *Loracarbef*.

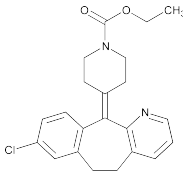
Assay preparation—Constitute 1 container of Loracarbef for Oral Suspension as directed in the labeling. Transfer an accurately measured volume of Loracarbef for Oral Suspension, freshly mixed and free from air bubbles, equivalent to about 200 mg of Loracarbef, to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a second 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass a portion of this solution through a filter having a porosity of 0.5 µm or finer, and use the filtrate as the *Assay preparation*.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Loracarbef*. Calculate the quantity, in mg, of anhydrous loracarbef ($C_{16}H_{16}ClN_3O_4$) in each mL of the Loracarbef for Oral Suspension taken by the formula:

$$(CP / V)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Loracarbef RS in the *Standard preparation; P* is the specified potency, in µg of anhydrous loracarbef ($C_{16}H_{16}ClN_3O_4$) per mg, of USP Loracarbef RS; *V* is the volume, in mL, of Loracarbef for Oral Suspension taken to prepare the *Assay preparation;* and r_U and r_S are the loracarbef peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Loratadine



$C_{22}H_{23}ClN_2O_2$ 382.88

1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester.

Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate [79794-75-5].

» Loratadine contains not less than 98.5 percent and not more than 101.0 percent of $C_{22}H_{23}ClN_2O_2$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store between 2° and 30°.

Labeling—If a test for *Related compounds* other than *Test 1* is used, then the labeling states with which *Related compounds* test the article complies.

USP Reference standards ⟨11⟩**—**

USP Loratadine RS

USP Loratadine Related Compound A RS
8-Chloro-6,11-dihydro-11(4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*] pyridine.
$C_{19}H_{19}ClN_2$ 310.83

USP Loratadine Related Compound B RS
8-Chloro-6,11-dihydro-11(*N*-methyl-4-piperinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.
$C_{20}H_{21}ClN_2$ 324.88

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Melting range ⟨741⟩**:** between 132° and 137°.

Loss on drying ⟨731⟩**—**Dry it at 100° to constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

Related compounds—

NOTE—On the basis of the synthetic route, perform either *Test 1* or *Test 2. Test 2* is recommended if 4,8-dichloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one is a potential related compound.

TEST 1—

Mobile phase and *Diluent*—Prepare as directed in the *Assay.*

Standard stock solution—Prepare as directed for *Standard preparation* in the *Assay.*

Standard solution—Pipet 5.0 mL of *Standard stock solution* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. Dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.8 µg per mL.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The column temperature is maintained between 25° and 35°. The flow rate is about 1 mL per minute. Chromatograph the *Test solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.79 for 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl and 1.0 for loratadine. Chromatograph the *Standard solution,* and record the peak area of the main peak as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure all the peak areas in the *Test solution* and the area of the main peak in the *Standard solution.* Calculate the percentage of each impurity in the portion of Loratadine taken by the formula:

$$10{,}000(C/F)(r_i / r_S)/W$$

in which C is the concentration, in mg per mL, of USP Loratadine RS in the *Standard solution; F* is the relative response factor for each impurity, if known (*F* is 0.25 for 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl); r_i is the peak area response for each impurity in the *Test solution;* r_S is the peak area response of loratadine in the *Standard solution;* and W is the quantity, in mg, of Loratadine taken to prepare the *Test solution:* not more than 0.2% of 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl is found; not more than 0.1% of any other

Related Compound	Relative Retention Time with respect to Loratadine	Relative Response Factor *(F)* with respect to Loratadine
Loratadine related compound A	0.50	1.00
Loratadine related compound B	0.53	0.89
8-Chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one	0.70	0.60
8-Chloro-6,11-dihydro-11-[*N*-methyl-4-piperidinyl]11-hydroxy-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine	0.75	0.46
4,8-Dichloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one	1.23	0.92
8-Chloro-6,11-dihydro-11-[*N*-ethoxy carbonyl-4-piperidinyl]-11-hydroxy-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine	1.60	0.42
4,8-Dichloro-6,11-dihydro-11-[*N*-ethoxy carbonyl-4-piperidylidene]-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine	1.83	1.08
Loratadine	1.00	1.00

individual impurity is found; and not more than 0.3% of total impurities is found.

TEST 2—

Solution A—Dissolve 0.96 g of 1-pentanesulfonic acid sodium salt in 900 mL of water. Adjust with phosphoric acid solution (1 in 10) to a pH of 3.00 ± 0.05, dilute with water to 1 L, filter, and degas.

Solution B—Use acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve accurately weighed quantities of USP Loratadine RS, USP Loratadine Related Compound A RS, and USP Loratadine Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution containing about 0.1 mg of each compound per mL. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, add 2 mL of *Solution A,* dilute with methanol to volume, and mix to obtain a solution having a known concentration of about 0.01 mg of each per mL.

Test solution—Transfer about 100 mg of Loratadine, accurately weighed, to a 10-mL volumetric flask, and dissolve in 2 mL of methanol. Add 2 mL of *Solution A,* then dilute with methanol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column containing 5-µm packing L1. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

Time (min)	*Solution A* (%)	*Solution B* (%)	Elution
0	75	25	isocratic
0–20	75→50	25→50	linear gradient
20–30	50→40	50→60	linear gradient
30–35	40→30	60→70	linear gradient
35–45	30	70	isocratic
45–50	30→75	70→25	step gradient

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times and response factors are as follows in the table below. The resolution, *R,* between loratadine related compound A and loratadine related compound B is not less than 1.5; and the relative standard deviation of the loratadine peak response from replicate injections is not more than 10%.

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Loratadine taken by the formula:

$$(100/F)(C_S / C_T)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Loratadine RS in the *Standard solution;* C_T is the concentration, in mg per mL of the *Test solution;* F is the relative response factor as indicated in the table (F = 1.0 for unknown impurities); r_i is the peak area response for the individual impurity in the *Test solution;* and r_S is the peak response for loratadine in the *Standard solution:* not more than 0.1% of loratadine related compound A is found; not more than 0.1% of loratadine related compound B is found; less than 0.1% for each individual unknown impurity is found; and not more than 0.3% of total impurities is found.

Assay—

0.01 M Dibasic potassium phosphate—Transfer about 1.74 g of anhydrous dibasic potassium phosphate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

0.6 M Dibasic potassium phosphate—Transfer 105 g of anhydrous dibasic potassium phosphate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Dibasic potassium phosphate,* methanol, and acetonitrile (7:6:6). Adjust with 10% phosphoric acid solution to an apparent pH of 7.2. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

0.05 N Hydrochloric acid—Transfer 500 mL of water to a 1000-mL volumetric flask, add 83 mL of hydrochloric acid, dilute with water to volume, and mix. Transfer 50 mL of this solution into a 1000-mL volumetric flask, dilute with water to volume, and mix.

Diluent—Transfer 400 mL of *0.05 N Hydrochloric acid* and 80 mL of *0.6 M Dibasic potassium phosphate* to a 1000-mL volumetric flask, dilute with a mixture of methanol and acetonitrile (1:1) to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Loratadine RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.4 mg per mL.

Assay preparation—Transfer about 40 mg of Loratadine, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm ×15-cm column that contains 5-µm packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained between 25° and 35°. Chromatograph the *Standard preparation,* and record the peak area responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{22}H_{23}ClN_2O_2$ in the portion of Loratadine taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Loratadine RS in the *Standard preparation;* and r_U and r_S are the peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Loratadine Oral Solution

DEFINITION

Loratadine Oral Solution contains NLT 94.0% and NMT 105.0% of the labeled amount of loratadine ($C_{22}H_{23}ClN_2O_2$).

IDENTIFICATION

- **A. Thin-Layer Chromatographic Identification Test ⟨201⟩**
  Standard solution: 5 mg/mL of USP Loratadine RS in dichloromethane
  Sample solution: Place a volume of Oral Solution, equivalent to 10 mg of loratadine, in a centrifuge tube. Add 10 mL of 0.2 N sodium hydroxide and 2.0 mL of dichloromethane. Rotate the centrifuge tube for 10 min, centrifuge, and discard the aqueous phase.
  Developing solvent system: Ethyl ether and diethylamine (40:1), in a paper-lined tank
  Acceptance criteria: Meets the requirements
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**
  Buffer: 6.8 g/L of monobasic potassium phosphate in water, adjusted with phosphoric acid to a pH of 3.0 ± 0.1
  Mobile phase: Acetonitrile and *Buffer* (3:7)
  Diluent: Acetonitrile and water (3:7)
  Internal standard solution: 0.3 mg/mL of butylparaben in *Diluent*
  Standard stock solution: 1.0 mg/mL of USP Loratadine RS in acetonitrile
  Standard solution: Transfer 5.0 mL of *Internal standard solution*, 5.0 mL of *Standard stock solution*, and 12 mL of water to a 50-mL volumetric flask. Dilute with *Diluent* to volume.
  Sample solution: Transfer a portion of Oral Solution, nominally equivalent to 5 mg of loratadine, to a 50-mL volumetric flask. Pipet 5.0 mL of *Internal standard solution* into the flask, and dilute with *Diluent* to volume.
  Chromatographic system
  (See *Chromatography* ⟨621⟩*, System Suitability*.)
  Mode: LC
  Detector: UV 254 nm
  Column: 4-mm × 30-cm; 10-µm packing L11
  Column temperature: 20°–30°
  Flow rate: 2 mL/min
  Injection size: 10 µL
  System suitability
  Sample: *Standard solution*
  [NOTE—The relative retention times for butylparaben and loratadine are about 0.78 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 1.9 between loratadine and butylparaben
  Tailing factor: NMT 1.6 for the loratadine and butylparaben peaks
  Relative standard deviation: NMT 2%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of loratadine ($C_{22}H_{23}ClN_2O_2$) in the portion of Oral Solution taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of loratadine to the internal standard from the *Sample solution*
R_S = peak response ratio of loratadine to the internal standard from the *Standard solution*
C_S = concentration of USP Loratadine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of loratadine in the *Sample solution* (mg/mL)

  Acceptance criteria: 94.0%–105.0%

PERFORMANCE TESTS

- **Deliverable Volume ⟨698⟩:** Meets the requirements

IMPURITIES

- **Organic Impurities**
  Mobile phase: 4.3 g/L of sodium dodecyl sulfate in a mixture of acetonitrile and water (1:1). Adjust with phosphoric acid to a pH of 2.6 ± 0.1.
  Diluent: *Mobile phase* and water (2:1)
  System suitability solution 1: 2 µg/mL of USP Loratadine RS in *Diluent*
  System suitability solution 2: 0.2 µg/mL of USP Loratadine RS in *Diluent* from *System suitability solution 1*
  System suitability solution 3: Transfer an amount of Oral Solution, equivalent to 20 mg of loratadine, into a screw-cap glass container. Add 1 mL of 3% aqueous hydrogen peroxide, and mix. Cap, and heat at 65° for 18–24 h. Allow to cool to room temperature, and then dilute 5 mL with *Diluent* to 25 mL.
  Sample solution: 0.2 mg/mL of loratadine from a volume of Oral Solution in *Diluent*
  Chromatographic system
  (See *Chromatography* ⟨621⟩*, System Suitability*.)
  Mode: LC
  Detector: UV 254 nm
  Column: 4.6-mm × 25-cm; 5-µm packing L7
  Column temperature: 30°–40°
  Flow rate: 2 mL/min
  Injection size: 50 µL
  System suitability
  Samples: *System suitability solution 1*, *System suitability solution 2*, and *System suitability solution 3*
  [NOTE—See *Table 1* for relative retention times.]
  Suitability requirements
  Resolution: NLT 3.0 between loratadine and 2-hydroxymethyl loratadine, *System suitability solution 3*
  Tailing factor: 0.7–1.1, *System suitability solution 1*
  Relative standard deviation: NMT 10%, *System suitability solution 2*
  Analysis
  Sample: *Sample solution*
  Calculate the percentage of each individual related compound in the portion of Oral Solution taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = individual peak response of each related compound in the *Sample solution*
r_T = sum of all the peak responses in the *Sample solution*, excluding excipient peaks