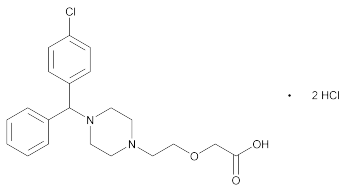
Add the following:

•Cetirizine Hydrochloride



$C_{21}H_{25}ClN_2O_3 \cdot 2HCl$ 461.81
(±)-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] acetic acid, dihydrochloride.
(±)-[2-[4-(*p*-Chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]acetic acid, dihydrochloride [*83881-52-1*].

» Cetirizine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, protected from light and moisture. Store at room temperature.

Labeling—Label it to indicate with which impurity procedures the article complies.

USP Reference standards ⟨11⟩**—***USP Cetirizine Hydrochloride RS. USP Cetirizine Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements of the test for *Chloride* ⟨191⟩.

pH ⟨791⟩**:** between 1.2 and 1.8, in an aqueous solution 1 in 20.

Loss on drying ⟨731⟩**—**Dry it at 105° to constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.2%.

Heavy metals, *Method I* ⟨231⟩**:** not more than 0.001%.

Related compounds—

TEST 1—

NOTE—It is recommended that *Test 2* be performed if either cetirizine ethanol (2-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}ethanol) or cetirizine acetic acid (2-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}acetic acid) may be present in the test substance.

Mobile phase—Proceed as directed in the *Assay*.

System suitability solution—Dissolve an accurately weighed quantity of USP Cetirizine Hydrochloride RS and USP Cetirizine Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having concentrations of about 4 µg per mL of USP Cetirizine Hydrochloride RS and about 4 µg per mL of USP Cetirizine Related Compound A RS.

Standard solution—Dissolve an accurately weighed quantity of USP Cetirizine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.5 µg per mL.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay*. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cetirizine related compound A and cetirizine is not less than 2.0; and the tailing factor for the cetirizine peak is not more than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. [NOTE—Record the chromatogram of the *Test solution* for a period of time equivalent to 3 times the retention time of cetirizine.] Calculate the percentage of each related compound in the portion of Cetirizine Hydrochloride taken by the formula:

$$0.1 \times (C_S / C_U) \times (1/F) \times (r_I / r_S)$$

in which C_S is the concentration, in µg per mL, of USP Cetirizine Hydrochloride RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Cetirizine Hydrochloride in the *Test solution;* F is the relative response factor as indicated in *Table 1*; r_i is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of cetirizine obtained from the *Standard solution.* The limits of impurities are as specified in *Table 1*.

Table 1

Compound Name	Approximate Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
4-CBH[1]	0.3	1.4	0.1
Dimer[2]	0.5	1.8	0.1
2-Chlorocetirizine[3]	0.85	0.49	0.1
Cetirizine related compound A[4]	0.9	0.95	0.1
Cetirizine	1.0	—	—
Deschlorocetirizine[5]	1.4	0.45	0.1
CBHP[6]	1.45	1.6	0.1
Individual unspecified impurity	—	1.0	0.1
Total	—	—	0.3

[1]4-Chlorobenzhydrol.
[2]1,4-Bis[(4-chlorophenyl)phenylmethyl]piperazine.
[3]2-[2-[4-[(2-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid.
[4]2-[2-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid, ethyl ester (cetirizine ethyl ester).
[5]2-[2-[4-(Diphenylmethyl]piperazin-1-yl]ethoxy]acetic acid.
[6]1-[(4-Chlorophenyl)phenylmethyl]piperazine.

[NOTE—Do not report peaks below 0.02%.]

TEST 2—

Solution A—Dissolve 2 g of tetrabutylammonium hydrogen sulfate and 3 g of sodium phosphate monobasic in 1 L of water, adjust with 1 N sodium hydroxide to a pH of 2.8 ± 0.05, filter, and degas.

Solution B—Methanol.

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⟩).

Diluent—Dissolve 1.4 g of sodium phosphate monobasic monohydrate and 2.7 g of sodium phosphate dibasic heptahydrate in 1 L of water, and adjust with either 1 N NaOH or 10% phosphoric acid to a pH of 6.9 ± 0.1. To 500 mL of this solution add 500 mL of acetonitrile.

Standard solution—Dissolve USP Cetirizine Hydrochloride RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution containing about 2 µg per mL of USP Cetirizine Hydrochloride RS.

Test solution—Transfer about 20 mg of cetirizine hydrochloride, accurately weighed, to a 10-mL volumetric flask, dissolve, and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 232-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (min)	*Solution A* (%)	*Solution B* (%)	Flow Rate (mL/min)	Elution
0	58	42	1.2	isocratic
40	58	42	1.2	isocratic
68	20	80	1.5	linear gradient
108	20	80	1.5	isocratic
110	58	42	1.2	linear gradient
120	58	42	1.2	isocratic

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the tailing factor of the cetirizine peak is not more than 2, the column efficiency is not less than 6000 theoretical plates, and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the percentage of each related compound in the portion of Cetirizine Hydrochloride taken by the formula:

$$0.1 \times (C_S / C_U) \times (1/F) \times (r_I / r_S)$$

in which C_S is the concentration, in µg per mL, of USP Cetirizine Hydrochloride RS in the *Standard solution;* C_U is the concentration, in mg per mL, of cetirizine hydrochloride in the *Test solution;* F is the relative response factor as indicated in *Table 2*; r_I is the peak response of each impurity obtained from the *Test solution*; and r_S is the peak response of cetirizine obtained from the *Standard solution*. The limits of impurities are as specified in *Table 2*.

Table 2

Compound Name	Approximate Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
Deschlorocetirizine[1]	0.35	0.56	0.1
Cetirizine ethanol[2]	0.53	1.2	0.1
CBHP [3]	0.66	1.3	0.1
2-Chlorocetirizine[4]	0.70	0.52	0.1
Cetirizine methyl ester[5]	0.81	0.96	0.1
3-Chlorocetirizine[6]	0.87	0.52	0.1
Cetirizine	1.0	—	—
Cetirizine acetic acid[7]	1.15	0.97	0.1
Cetirizine *N*-oxide[8]	1.25	0.81	0.1
4-CBH[9]	1.55	1.2	0.1
4-Chlorobenzophenone[10]	1.66	0.50	0.1
Cetirizine dimer[11]	2.48	1.4	0.1
Individual unknown impurity	—	1.0	0.10
Total	—	—	0.3

[1]2-{2-[4-(Diphenylmethyl)piperazin-1-yl]ethoxy}acetic acid.
[2]2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}ethanol.
[3]1-[(4-Chlorophenyl)phenylmethyl]piperazine.
[4]2-(2-{4-[(2-Chlorophenyl)phenylmethyl]piperazin-1-yl}ethoxy)acetic acid.
[5]Methyl 2-(2-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}ethoxy)acetate.
[6]2-[2-[4-[(3-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid.
[7]2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}acetic acid.
[8]2-(2-{4-[(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetic acid N^1-oxide.
[9]4-Chlorobenzhydrol.
[10](4-Chlorophenyl)phenylmethanone.
[11]1,4-Bis[(4-chlorophenyl)phenylmethyl]piperazine.

[NOTE—Do not report peaks below 0.05%.]

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, and 1 M sulfuric acid (93 : 6.6 : 0.4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Cetirizine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Cetirizine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L3. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the cetirizine peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the cetirizine peaks. Calculate the quantity, in mg, of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$ in the portion of Cetirizine Hydrochloride taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Cetirizine Hydrochloride RS in the *Standard preparation*; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.●(RB 1-May-2010)