

**Impurity Table 1** (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Henicosenyl leucinate <sup>d</sup>	4.7	2.3	0.3
Any other identified impurity	—	—	0.3
Individual unidentified impurity	—	1.0	0.2
Total impurities	—	—	3.0

<sup>a</sup> (2*S*,3*R*,5*S*)-5-[(*N*-Formyl-L-leucyl)oxy]-2-hexyl-3-hydroxyhexadecanoic acid.

<sup>b</sup> (2*S*,3*S*,5*S*)-5-[(*N*-Formyl-L-leucyl)oxy]-2-hexyl-3-hydroxyhexadecanoic acid.

<sup>c</sup> (5*S*)-3-Hexyl-5,6-dihydro-6-undecyl-2*H*-pyran-2-one.

<sup>d</sup> (5*S*)-[(5*E*)-Henicos-7-en-10-yl] *N*-formyl-L-leucinate.

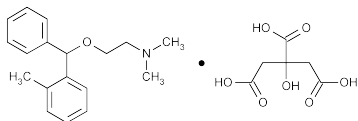
**ADDITIONAL REQUIREMENTS**

• **PACKAGING AND STORAGE:** Preserve in tight containers, and store at 25°, excursions permitted between 15° and 30°.

• **USP REFERENCE STANDARDS** (11)

USP Orlistat RS

USP Orlistat Related Compound D RS▲<sup>USP35</sup>

**Orphenadrine Citrate**

$C_{18}H_{23}NO \cdot C_6H_8O_7$  461.50

Ethanamine, *N,N*-dimethyl-2-[(2-methylphenyl)phenylmethoxy]-, (±)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

(±)-*N,N*-Dimethyl-2-[(*o*-methyl- $\alpha$ -phenylbenzyl)oxy]ethylamine citrate (1:1) [4682-36-4].

» Orphenadrine Citrate contains not less than 98.0 percent and not more than 101.5 percent of  $C_{18}H_{23}NO \cdot C_6H_8O_7$ , calculated on the dried basis.

**Packaging and storage**—Preserve in tight, light-resistant containers.

**USP Reference standards** (11)—

USP Orphenadrine Citrate RS

**Clarity and color of solution**—Mix 1 g of it with 10 mL of a 1 in 28 solution of hydrochloric acid in alcohol: the solution is clear and its absorbance at 436 nm is not greater than 0.050.

**Identification**—

**A:** Infrared Absorption (197M).

**B:** Ultraviolet Absorption (197U)—

**Solution:** 500  $\mu$ g per mL.

**Medium:** alcohol.

Absorptivities at 264 nm, calculated on the dried basis, do not differ by more than 3.0%.

**Melting range** (741): between 134° and 138°.

**Loss on drying** (731)—Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

**Residue on ignition** (281): not more than 0.1%.

**Related compounds**—

0.05 *M* Ammonium phosphate buffer, Mobile phase, System sensitivity solution, and Chromatographic system—Prepare as directed in the Assay.

**Standard solution**—Use the *Standard preparation*, prepared as directed in the Assay.

**Test solution**—Use the *Assay preparation*, prepared as directed in the Assay.

**Procedure**—Separately inject equal volumes (about 20  $\mu$ L) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatogram for at least 2.5 times the retention time of orphenadrine citrate, and measure all of the peak areas. Calculate the percentage of each impurity in the portion of Orphenadrine Citrate taken by the formula:

$$5000F(C/W)(r_i/r_s)$$

in which *C* is the concentration, in mg per mL, of USP Orphenadrine Citrate RS in the *Standard solution*; *W* is the weight, in mg, of the sample taken to prepare the *Test solution*; *F* is the relative response factor described in the table below; *r<sub>i</sub>* is the peak area for each impurity in the *Test solution*; and *r<sub>s</sub>* is the peak area of Orphenadrine Citrate in the *Standard solution*: not more than 0.5% of total impurities is found.

Compound name	Relative Retention Time	Relative Response Factor
Ethylidimethyl [2-(2-methylbenzhydryloxy)ethyl] ammonium chloride	0.25	0.75
2-Methylbenzhydrol	0.51	0.41
Orphenadrine Citrate	1.0	—
<i>N,N</i> -Dimethyl-2-( <i>o</i> -tolyl- <i>o</i> -xylyloxy)ethylamine	1.54	0.52
Others	—	1.0

**Isomer content**—

**Solvent**—Use carbon tetrachloride.

**NMR reference**—Use tetramethylsilane.

**Test preparation**—Place about 1 g of Orphenadrine Citrate and 10 mL of water in a 60-mL separator, slowly add about 20 drops of sodium hydroxide solution (1 in 2), with swirling, to obtain a solution having a pH of about 10, and extract with three 15-mL portions of ether. Combine the ether extracts in a beaker, discarding the aqueous phase, and evaporate to about one-half the volume by warming on a steam bath under a stream of nitrogen. Transfer to a 60-mL separator, wash with three 20-mL portions of water, and dry the ether solution with about 15 g of anhydrous sodium sulfate in a 125-mL conical flask for 1 hour, with intermittent swirling. Decant the dried ether solution through a pledget of glass wool into a small beaker. Rinse the sodium sulfate with two 10-mL portions of ether, and add the rinsings to the beaker. Evaporate most of the ether by warming under a stream of nitrogen, and remove the last traces of ether by drying at a pressure not exceeding 2 mm of mercury at 60°. Transfer 400 mg of the orphenadrine so obtained to a small weighing bottle, add 0.5 mL of carbon tetrachloride and 1 drop of tetramethylsilane, and swirl to dissolve.

**Procedure**—Proceed as directed for *Relative Method of Quantitation* under *Nuclear Magnetic Resonance* (761), using the calculation formula given therein, in which *A<sub>i</sub>* is the sum of the average areas of the combined methine peaks associated with the *meta*- and *para*-methylbenzyl isomers, appearing at about 5.23 ppm, and *A<sub>2</sub>* is the area of the methine peak associated with the *ortho*-methylbenzyl isomer, appearing at about 5.47 ppm, with reference to the tetramethylsilane singlet at 0 ppm, and both *n<sub>1</sub>* and *n<sub>2</sub>* are equal to 1: the limit of combined *meta*- and *para*-methylbenzyl isomers is 3.0%.

**Assay**—

0.05 *M* Ammonium phosphate buffer—Dissolve 5.8 g of monobasic ammonium phosphate in 1000 mL of water, and adjust with ammonium hydroxide or phosphoric acid to a pH of 7.9  $\pm$  0.05.

**Mobile phase**—Prepare a filtered and degassed mixture of methanol, 0.05 M Ammonium phosphate buffer, and acetonitrile (9:8:3). Make adjustments if necessary (see *System Suitability* under *Chromatography* <621>).

**Standard preparation**—Dissolve an accurately weighed quantity of USP Orphenadrine Citrate RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.9 mg per mL.

**System sensitivity solution**—Dilute a volume of the *Standard preparation* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.00045 mg per mL.

**Assay preparation**—Transfer about 45 mg of Orphenadrine Citrate, accurately weighed, to a 50-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 220-nm detector and a 4.6-mm × 15-cm column that contains 5-μm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard preparation*, and record the peak areas as directed for *Procedure*: the column efficiency is not less than 4500 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *System sensitivity solution*, and record the peak areas as directed for *Procedure*: the signal-to-noise ratio is not less than 10.

**Procedure**—Separately inject equal volumes (about 20 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas for orphenadrine citrate. Calculate the quantity, in mg, of C<sub>18</sub>H<sub>23</sub>NO · C<sub>6</sub>H<sub>8</sub>O<sub>7</sub> in the portion of Orphenadrine Citrate taken by the formula:

$$50C(r_u / r_s)$$

in which *C* is the concentration, in mg per mL, of USP Orphenadrine Citrate RS in the *Standard preparation*; and *r<sub>u</sub>* and *r<sub>s</sub>* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

## Orphenadrine Citrate Injection

» Orphenadrine Citrate Injection is a sterile solution of Orphenadrine Citrate in Water for Injection, prepared with the aid of Sodium Hydroxide. It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of orphenadrine citrate (C<sub>18</sub>H<sub>23</sub>NO · C<sub>6</sub>H<sub>8</sub>O<sub>7</sub>).

**Packaging and storage**—Preserve in single-dose or multiple-dose containers, preferably of Type I glass, protected from light.

### USP Reference standards <11>—

USP Endotoxin RS  
USP Orphenadrine Citrate RS

### Identification—

**A:** 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*.

**B:** A few drops of Injection respond to the test for *Citrate* <191>.

**Bacterial endotoxins** <85>—It contains not more than 5.8 USP Endotoxin Units per mg of orphenadrine citrate.

**pH** <791>: between 5.0 and 6.0.

### Related compounds—

0.05 M Ammonium phosphate buffer, *Mobile phase*, *System sensitivity solution*, and *Chromatographic system*—Prepare as directed in the *Assay*.

**Standard solution**—Use the *Standard preparation*, prepared as directed in the *Assay*.

**Test solution**—Use the *Assay preparation*, prepared as directed in the *Assay*.

**Procedure**—Separately inject equal volumes (about 20 μL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatogram for at least 2.5 times the retention time of orphenadrine citrate, and measure all of the peak areas. Calculate the percentage of each impurity in the portion of Injection taken by the formula:

$$(10,000F)(C/V)(1/D)(r_i / r_s)$$

in which *F* is the relative response factor as found in the table below; *C* is the concentration, in mg per mL, of USP Orphenadrine Citrate RS in the *Standard solution*; *V* is the volume, in mL, of Injection taken to prepare the *Test solution*; *D* is the labeled dose of Injection; *r<sub>i</sub>* is the peak area for each impurity in the *Test solution*; and *r<sub>s</sub>* is the peak area of Orphenadrine Citrate in the *Standard solution*: not more than 4.0% of total impurities is found.

Compound name	Relative Retention Time	Relative Response Factor
Ethylidimethyl [2-(2-methylbenzhydryloxy)ethyl] ammonium chloride	0.25	0.75
2-Methylbenzhydrol	0.51	0.41
Orphenadrine Citrate	1.0	—
N,N-Dimethyl-2-(o-tolyl-o-xylyloxy)ethylamine	1.54	0.52
Others	—	1.0

**Other requirements**—It meets the requirements under *Injections* <1>.

### Assay—

0.05 M Ammonium phosphate buffer—Dissolve 5.8 g of monobasic ammonium phosphate in 1000 mL of water, and adjust with ammonium hydroxide or phosphoric acid to a pH of 7.9 ± 0.05.

**Mobile phase**—Prepare a filtered and degassed mixture of methanol, 0.05 M Ammonium phosphate buffer, and acetonitrile (9:8:3). Make adjustments if necessary (see *System Suitability* under *Chromatography* <621>).

**Standard preparation**—Dissolve an accurately weighed quantity of USP Orphenadrine Citrate RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.9 mg per mL.

**System sensitivity solution**—Dilute a volume of the *Standard preparation* quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.00045 mg per mL.

**Assay preparation**—Transfer an accurately measured volume of Injection, equivalent to about 90 mg of orphenadrine citrate, to a 100-mL volumetric flask, dilute with water to volume, and mix.

**Chromatographic system** (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 5-μm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard preparation*, and record the peak areas as directed for *Procedure*: the column efficiency is not less than 4500 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation