

- r_s = peak response of the related compound from the *Standard solution*
 W_i = weight of the respective USP Reference Standard taken to prepare the *Standard solution* (mg)
 W_U = weight of Tioconazole taken to prepare the *Sample solution* (mg)

Acceptance criteria: The limit of each related compound is NMT 1.0%.

SPECIFIC TESTS

- **WATER DETERMINATION, Method I (921):** NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **USP REFERENCE STANDARDS (11)**
 - USP Tioconazole RS
 - USP Tioconazole Related Compound A RS
1-[2,4-Dichloro- β -(3-thenyl)-oxy]phenethyl]imidazole hydrochloride.
 $C_{16}H_{14}Cl_2N_2OS \cdot HCl$ 389.73
 - USP Tioconazole Related Compound B RS
1-[2,4-Dichloro- β -(2,5-dichloro-3-thenyl)oxy]phenethyl]imidazole hydrochloride.
 $C_{16}H_{12}Cl_4N_2OS \cdot HCl$ 458.62
 - USP Tioconazole Related Compound C RS
1-[2,4-Dichloro- β -(5-bromo-2-chloro-3-thenyl)-oxy]phenethyl]imidazole hydrochloride.
 $C_{16}H_{13}BrCl_2N_2OS \cdot HCl$ 468.63

Titanium Dioxide

TiO_2 79.87

Titanium oxide (TiO_2).

Titanium oxide (TiO_2) [13463-67-7].

» Titanium Dioxide contains not less than 99.0 percent and not more than 100.5 percent of TiO_2 , calculated on the dried basis. If labeled as attenuation grade, then Titanium Dioxide contains not less than 99.0 percent and not more than 100.5 percent of TiO_2 , calculated on the ignited basis. Attenuation grade material may contain suitable coatings, stabilizers, and treatments to assist formulation.

NOTE—If labeled as attenuation grade, then all tests and assays are conducted on uncoated, untreated material. For UV attenuation grade, the test for *Loss on drying* does not apply. The FDA requires the content of lead to be not more than 10 ppm, that of antimony to be not more than 2 ppm, and that of mercury to be not more than 1 ppm (21 CFR 73.1575).

Packaging and storage—Preserve in well-closed containers.

Labeling—If intended for UV-attenuation, the material must be labeled as attenuation grade. If intended for UV-attenuation, and any added coatings, stabilizers, or treatments are used, the labeling shall include the name and amount of the additives.

Identification—To 500 mg add 5 mL of sulfuric acid, and heat gently. After fumes of sulfur trioxide appear, continue heating for a minimum of 10 seconds. Cool the suspension, and cautiously dilute with water to 100 mL. Filter, and to 5 mL of the clear filtrate add a few drops of hydrogen peroxide TS: a yellow-red to orange-red color develops immediately.

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

Loss on ignition (733)—Ignite 2 g, previously dried and accurately weighed, at $800 \pm 25^\circ$ to constant weight: it loses not

more than 0.5% of its weight. If labeled as attenuation grade, ignite 4 g of titanium dioxide, accurately weighed, at $800 \pm 25^\circ$ to constant weight: it loses not more than 13% of its weight.

Water-soluble substances—Suspend 4.0 g in 50 mL of water, mix, and allow to stand overnight. Transfer to a 200-mL volumetric flask, add 2 mL of ammonium chloride TS, and mix. If the Titanium Dioxide does not settle, add another 2-mL portion of ammonium chloride TS. Allow the suspension to settle, dilute with water to volume, mix, and filter through a double thickness of fine-porosity filter paper, discarding the first 10 mL of the filtrate. Collect 100 mL of the clear filtrate, transfer to a tared platinum dish, evaporate on a hot plate to dryness, and ignite at a dull red heat to constant weight: the residue weighs not more than 5 mg (0.25%).

Acid-soluble substances—Suspend 5.0 g in 100 mL of 0.5 N hydrochloric acid, and heat on a steam bath for 30 minutes, with occasional stirring. Filter through an appropriate filter medium until clear. Wash with three 10-mL portions of 0.5 N hydrochloric acid. Evaporate the combined filtrate and washings to dryness, and ignite at a dull red heat to constant weight: the residue weighs not more than 25 mg (0.5%).

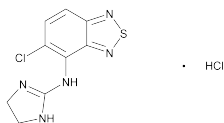
Arsenic, Method I (211)—Prepare the *Test Preparation* as follows. Add 3.0 g to a 250-mL conical flask fitted with a thermometer and a vapor outlet. Add 50 mL of water, 500 mg of hydrazine sulfate, 500 mg of potassium bromide, 20 g of sodium chloride, and 25 mL of sulfuric acid. Arrange to collect the evolved vapors in 52 mL of water contained in the arsine generator flask, then heat the test specimen to 90° , and maintain the temperature at 90° to 100° for 15 minutes. Add 3 mL of hydrochloric acid to the solution in the generator flask: the resulting solution meets the requirements of the test, the addition of 20 mL of 7 N sulfuric acid specified for *Procedure* being omitted. The limit is 1 ppm.

Assay—Accurately weigh about 300 mg of Titanium Dioxide, transfer to a 250-mL beaker, and add 20 mL of sulfuric acid and 7 to 8 g of ammonium sulfate. Mix, heat on a hot plate until fumes of sulfur trioxide appear, and continue heating over a strong flame until solution is complete or it is apparent that the undissolved residue is siliceous matter. Cool, cautiously dilute with 100 mL of water, stir, heat carefully to boiling while stirring, and allow the insoluble matter to settle. Filter, transfer the entire residue to the filter, and wash thoroughly with cold 2 N sulfuric acid. Dilute the filtrate with water to 200 mL, and cautiously add about 10 mL of ammonium hydroxide.

Prepare a zinc amalgam column in a 25-cm Jones reductor tube, placing a pledget of glass wool in the bottom of the tube, and filling the constricted portion of the tube with zinc amalgam prepared as follows. Add 20- to 30-mesh zinc to mercuric chloride solution (1 in 50), using about 100 mL of the solution for each 100 g of zinc, and after about 10 minutes, decant the solution from the zinc, then wash the zinc by decantation. Wash the zinc amalgam column with 100-mL portions of 2 N sulfuric acid until 100 mL of the washing does not decolorize 1 drop of 0.1 N potassium permanganate.

Place 50 mL of ferric ammonium sulfate TS in a 1000-mL suction flask, and add 0.1 N potassium permanganate until a faint pink color persists for 5 minutes. Attach the Jones reductor tube to the neck of the flask, and pass 50 mL of 2 N sulfuric acid through the reductor at a rate of about 30 mL per minute. Pass the prepared titanium solution through the reductor at the same rate, and follow with 100 mL each of 2 N sulfuric acid and of water. During these operations, keep the reductor filled with solution or water above the upper level of the amalgam. Taking precautions against the admission of atmospheric oxygen, gradually release the suction, wash down the outlet tube of the reductor and the sides of the receiver, and titrate immediately with 0.1 N potassium permanganate VS. Perform a blank determination, substituting 200 mL of 2 N sulfuric acid for the assay solution, and make any necessary correction. Each mL of 0.1 N potassium permanganate is equivalent to 7.988 mg of TiO_2 .

Tizanidine Hydrochloride



$C_9H_8ClN_5S \cdot HCl$ 290.17

2,1,3-Benzothiadiazol-4-amine, 5-chloro-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-, monohydrochloride.

5-Chloro-4-(2-imidazol-2-ylamino)-2,1,3-benzothiadiazole monohydrochloride [64461-82-1].

» Tizanidine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_9H_8ClN_5S \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards (11)—

USP Tizanidine Hydrochloride RS

USP Tizanidine Related Compound A RS

4-Amino-5-chloro-2,1,3-benzothiadiazole.

$C_6H_4ClN_3S$ 185.63

USP Tizanidine Related Compound B RS

N-Acetyltizanidine.

$C_{11}H_{10}ClN_5OS$ 295.75

USP Tizanidine Related Compound C RS

1-Acetylimidazol-2-thione.

$C_5H_8N_2OS$ 144.20

Identification—

A: *Infrared Absorption* (197K).

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*.

C: A solution of 10 mg per mL in water meets the requirements of the silver nitrate precipitate test for *Chloride* (191).

pH (791): between 4.3 and 5.3, in a 1% (w/v) solution.

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

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

Heavy metals (231): 0.002%.

Related compounds—

Phosphoric acid solution—Transfer 6.0 mL of phosphoric acid to a 50-mL volumetric flask, and dilute with water to volume.

Buffer solution—Dissolve about 3.5 g of sodium 1-pentanesulfonate in 1000 mL of water, and adjust with *Phosphoric acid solution* or 1 N sodium hydroxide to a pH of 3.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Tizanidine related compound A solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Tizanidine related compound B solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Tizanidine related compound C solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound C RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Resolution solution—Transfer about 23 mg of USP Tizanidine Hydrochloride RS to a 100-mL volumetric flask, add 20 mL of *Mobile phase* and 10 mL each of *Tizanidine related compound A solution*, *Tizanidine related compound B solution*, and *Tizanidine related compound C solution*. Sonicate to dissolve the USP Tizanidine Hydrochloride RS, and dilute with *Mobile phase* to volume.

Standard solution—Dissolve an accurately weighed quantity of USP Tizanidine Hydrochloride RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.046 mg per mL.

Test solution—Transfer about 57 mg of Tizanidine Hydrochloride, 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 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 50°. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure*: the relative retention times are given in *Table 1*; the resolution, *R*, between tizanidine and tizanidine related compound C is not less than 4.0; and the resolution, *R*, between tizanidine and tizanidine related compound B is not less than 4.0. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the column efficiency is not less than 5000 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%.

Procedure—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 the major analyte peaks, disregarding the peaks due to the solvent. Calculate the percentage of each impurity in the portion of Tizanidine Hydrochloride taken by the formula:

$$(253.71/290.17)100(C_S / C_T)(1/F)(r_i / r_S)$$

in which 253.71 and 290.17 are the molecular weights of tizanidine and tizanidine hydrochloride, respectively; C_S and C_T are the concentration, in mg per mL, of tizanidine hydrochloride in the *Standard solution* and the *Test solution*; *F* is the relative response factor for each impurity relative to tizanidine and is given in *Table 1*; r_i is the peak area for each impurity obtained from the *Test solution*; and r_S is the peak area of tizanidine obtained from the *Standard solution*. The limits for the impurities are specified in *Table 1*.

Table 1

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
Tizanidine related compound C	about 0.8	1.0	0.1
Tizanidine	1.0	—	—
Tizanidine related compound B	about 1.4	1.1	0.1
Tizanidine related compound A	about 10.2	1.1	0.1
Individual unknown	—	1.0	0.1
Total	—	—	0.3

Assay—

Buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 5.3 N potassium hydroxide to a pH of 7.5 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).