– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

Solvent mixture: *water R, methanol R* (10:90 *V/V*).

Dissolve 0.50 g of the substance to be examined in 20 mL of the solvent mixture using sonication for about 10 min. The solution complies with test H. Prepare the reference solution using 0.5 mL of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): 2.5 per cent to 4.0 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

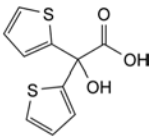
Dissolve 0.35 g in 100 mL of *water R*. Add 10 mL of *dilute nitric acid R2*. Titrate with *0.1 M silver nitrate* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 47.24 mg of $C_{19}H_{22}BrNO_4S_2$.

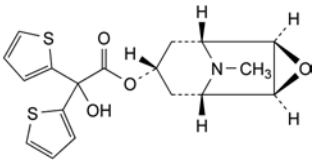
IMPURITIES

Specified impurities: A, C, E, F, G, H.

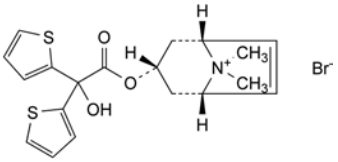
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *B, D, I, J, K.*



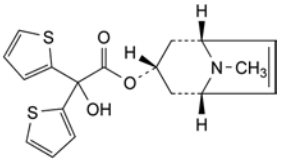
A. 2-hydroxy-2,2-dithiophen-2-ylacetic acid,



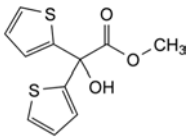
B. (1*R*,2*R*,4*S*,5*S*,7*s*)-9-methyl-3-oxa-9-azatricyclo [3.3.1.$0^{2,4}$]nonan-7-yl 2-hydroxy-2,2-dithiophen-2-ylacetate,



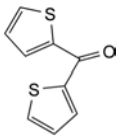
C. (1*R*,3*s*,5*S*)-3-[(2-hydroxy-2,2-dithiophen-2-ylacetyl)oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-6-ene bromide,



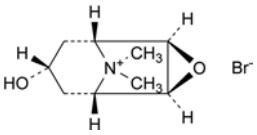
D. (1*R*,3*s*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-6-en-3-yl 2-hydroxy-2,2-dithiophen-2-ylacetate,



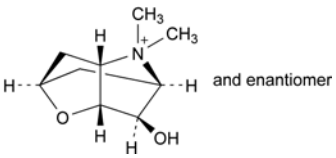
E. methyl 2-hydroxy-2,2-dithiophen-2-ylacetate,



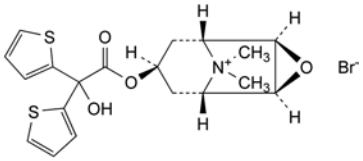
F. dithiophen-2-ylmethanone,



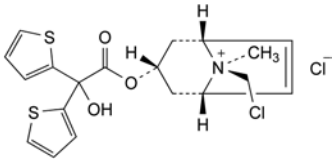
G. (1*R*,2*R*,4*S*,5*S*,7*s*)-7-hydroxy-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide,



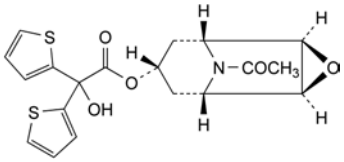
H. (1*s*,3*RS*,4*RS*,5*RS*,7*SR*)-4-hydroxy-6,6-dimethyl-2-oxa-6-azoniatricyclo[3.3.1.$0^{3,7}$]nonane bromide,



I. (1*R*,2*R*,4*S*,5*S*,7*r*)-7-[(2-hydroxy-2,2-dithiophen-2-ylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo [3.3.1.$0^{2,4}$]nonane bromide,



J. (1*R*,3*s*,5*S*,8*s*)-8-(chloromethyl)-3-[(2-hydroxy-2,2-dithiophen-2-ylacetyl)oxy]-8-methyl-8-azoniabicyclo[3.2.1]oct-6-ene chloride,



K. (1*R*,2*R*,4*S*,5*S*,7*s*)-9-acetyl-3-oxa-9-azatricyclo [3.3.1.$0^{2,4}$]nonan-7-yl 2-hydroxy-2,2-dithiophen-2-ylacetate.

01/2011:0150

TITANIUM DIOXIDE

Titanii dioxidum

TiO_2 M_r 79.9
[13463-67-7]

DEFINITION

Content: 98.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water. It does not dissolve in dilute mineral acids but dissolves slowly in hot concentrated sulfuric acid.

IDENTIFICATION

A. When strongly heated, it becomes pale yellow; the colour disappears on cooling.

B. To 5 mL of solution S2 (see Tests) add 0.1 mL of *strong hydrogen peroxide solution R*. An orange-red colour appears.

C. To 5 mL of solution S2 add 0.5 g of *zinc R* in granules. After 45 min, the mixture has a violet-blue colour.

TESTS

Solution S1. Shake 20.0 g with 30 mL of *hydrochloric acid R* for 1 min. Add 100 mL of *distilled water R* and heat the mixture to boiling. Filter the hot mixture through a hardened filter paper until a clear filtrate is obtained. Wash the filter with 60 mL of *distilled water R* and dilute the combined filtrate and washings to 200 mL with *distilled water R*.

Solution S2. Mix 0.500 g (*m* g) with 5 g of *anhydrous sodium sulfate R* in a 300 mL long-necked combustion flask. Add 10 mL of *water R* and mix. Add 10 mL of *sulfuric acid R* and boil vigorously, with the usual precautions, until a clear solution is obtained. Cool, add slowly a cooled mixture of 30 mL of *water R* and 10 mL of *sulfuric acid R*, cool again and dilute to 100.0 mL with *water R*.

Appearance of solution. Solution S2 is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

Acidity or alkalinity. Shake 5.0 g with 50 mL of *carbon dioxide-free water R* for 5 min. Centrifuge or filter until a clear solution is obtained. To 10 mL of the solution add 0.1 mL of *bromothymol blue solution R1*. Not more than 1.0 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Water-soluble substances: maximum 0.5 per cent.

To 10.0 g add a solution of 0.5 g of *ammonium sulfate R* in 150 mL of *water R* and boil for 5 min. Cool, dilute to 200 mL with *water R* and filter until a clear solution is obtained. Evaporate 100 mL of the solution to dryness in a tared evaporating dish and ignite. The residue weighs a maximum of 25 mg.

Antimony: maximum 100 ppm.

To 10 mL of solution S2 add 10 mL of *hydrochloric acid R* and 10 mL of *water R*. Cool to 20 °C, if necessary, and add 0.15 mL of *sodium nitrite solution R*. After 5 min, add 5 mL of a 10 g/L solution of *hydroxylamine hydrochloride R* and 10 mL of a freshly prepared 0.1 g/L solution of *rhodamine B R*. Mix thoroughly after each addition. Shake vigorously with 10.0 mL of *toluene R* for 1 min. Allow to separate and centrifuge for 2 min if necessary. Any pink colour in the toluene phase is not more intense than that in the toluene phase of a standard prepared at the same time in the same manner using a mixture of 5.0 mL of *antimony standard solution (1 ppm Sb) R*, 10 mL of *hydrochloric acid R* and 15 mL of a solution containing 0.5 g of *anhydrous sodium sulfate R* and 2 mL of *sulfuric acid R* instead of the mixture of 10 mL of solution S2, 10 mL of *hydrochloric acid R* and 10 mL of *water R*.

Arsenic (*2.4.2, Method A*): maximum 5 ppm.

Place 0.50 g in a 250 mL round-bottomed flask, fitted with a thermometer, a funnel with stopcock and a vapour-outlet tube connected to a flask containing 30 mL of *water R*. Add 50 mL of *water R*, 0.5 g of *hydrazine sulfate R*, 0.5 g of *potassium bromide R* and 20 g of *sodium chloride R*. Through the funnel, add dropwise 25 mL of *sulfuric acid R*, heat and maintain the temperature of the liquid at 110-115 °C for 20 min. Collect the vapour in the flask containing 30 mL of *water R*. Dilute to 50 mL with *water R*. 20 mL of the solution complies with the test.

Barium. To 10 mL of solution S1 add 1 mL of *dilute sulfuric acid R*. After 30 min, any opalescence in the solution is not more intense than that in a mixture of 10 mL of solution S1 and 1 mL of *distilled water R*.

Iron: maximum 200 ppm.

To 8 mL of solution S2 add 4 mL of *water R*. Mix and add 0.05 mL of *bromine water R*. Allow to stand for 5 min and remove the excess of bromine with a current of air. Add 3 mL of *potassium thiocyanate solution R*. Any colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using a mixture of 4 mL of *iron standard solution (2 ppm Fe) R* and 8 mL of a 200 g/L solution of *sulfuric acid R*.

Heavy metals (*2.4.8*): maximum 20 ppm.

To 10 mL of solution S1, add dropwise *concentrated ammonia R* to adjust to pH 4 and dilute to 20 mL with *water R*. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

ASSAY

To 300 g of *zinc R* in granules (710) add 300 mL of a 20 g/L solution of *mercuric nitrate R* and 2 mL of *nitric acid R*, shake for 10 min and wash with *water R*. Pack the amalgamated zinc into a glass tube about 400 mm long and about 20 mm in diameter fitted with a tap and a filter plate. Pass through the column 100 mL of *dilute sulfuric acid R* followed by 100 mL of *water R*, making sure that the amalgam is always covered with liquid. Pass slowly at a rate of about 3 mL/min through the column a mixture of 100 mL of *dilute sulfuric acid R* and 100 mL of *water R* followed by 100 mL of *water R*. Collect the eluate in a 500 mL conical flask containing 50.0 mL of a 150 g/L solution of *ferric ammonium sulfate R* in a mixture of 1 volume of *sulfuric acid R* and 3 volumes of *water R*. Add 0.1 mL of *ferroin R* and titrate immediately with *0.1 M ammonium and cerium nitrate* until a greenish colour is obtained (n_1 mL). Pass slowly at a rate of about 3 mL/min through the column a mixture of 50 mL of *dilute sulfuric acid R* and 50 mL of *water R*, followed by 20.0 mL of solution S2, a mixture of 50 mL of *dilute sulfuric acid R* and 50 mL of *water R* and finally 100 mL of *water R*. Collect the eluate in a 500 mL conical flask containing 50.0 mL of a 150 g/L solution of *ferric ammonium sulfate R* in a mixture of 1 volume of *sulfuric acid R* and 3 volumes of *water R*. Rinse the lower end of the column with *water R*, add 0.1 mL of *ferroin R* and titrate immediately with *0.1 M ammonium and cerium nitrate* until a greenish colour is obtained (n_2 mL).

Calculate the percentage content of TiO_2 using the following expression:

$$\frac{3.99 \times (n_2 - n_1)}{m}$$

m = mass of the substance to be examined used for the preparation of solution S2, in grams.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being

Monographs T-Z

suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for titanium dioxide used as opacifier in solid oral dosage forms and in preparations for cutaneous application.

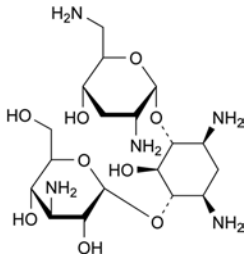
Particle-size distribution (*2.9.31*).

Bulk and tapped density (*2.9.34*).

01/2008:0645
corrected 6.2

TOBRAMYCIN

Tobramycinum



$C_{18}H_{37}N_5O_9$ M_r 467.5
[32986-56-4]

DEFINITION

4-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-6-*O*-(2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl)-L-streptamine.

Substance produced by *Streptomyces tenebrarius* or obtained by any other means.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is produced by methods of manufacture designed to eliminate or minimise substances lowering blood pressure.

CHARACTERS

Appearance: white or almost white powder.

Solubility: freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Nuclear magnetic resonance spectrometry (*2.2.33*).

Preparation: 100 g/L solution in *deuterium oxide R*.

Comparison: 100 g/L solution of *tobramycin CRS* in *deuterium oxide R*.

B. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 20 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution (a). Dissolve 20 mg of *tobramycin CRS* in *water R* and dilute to 5 mL with the same solvent.

Reference solution (b). Dissolve 4 mg of *neomycin sulfate CRS* and 4 mg of *kanamycin monosulfate CRS* in 1 mL of reference solution (a).

Plate: *TLC silica gel plate R*.

Mobile phase: *methylene chloride R, concentrated ammonia R, methanol R* (17:33:50 *V/V/V*).

Application: 5 µL.

Development: over 2/3 of the plate.

Drying: in a current of warm air.

Detection: spray with a mixture of equal volumes of a 2 g/L solution of *1,3-dihydroxynaphthalene R* in *ethanol (96 per cent) R* and a 460 g/L solution of *sulfuric acid R*; heat at 105 °C for 5-10 min.

System suitability: the chromatogram obtained with reference solution (b) shows 3 major spots which are clearly separated.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 5 mg in 5 mL of *water R*. Add 5 mL of a 1 g/L solution of *ninhydrin R* in *ethanol (96 per cent) R* and heat in a water-bath for 3 min. A violet-blue colour develops.

TESTS

pH (*2.2.3*): 9.0 to 11.0.

Dissolve 1.0 g in 10 mL of *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*): + 138 to + 148 (anhydrous substance).

Dissolve 1.00 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Test solution (b). Dilute 10.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (a). Dissolve 25.0 mg of *tobramycin CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c). Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Reference solution (d). Dissolve 10.0 mg of *kanamycin B sulfate CRS* in 20.0 mL of the mobile phase. To 1.0 mL of this solution, add 2.0 mL of reference solution (a) and dilute to 10.0 mL with the mobile phase.

Reference solution (e). Dilute 10.0 mL of reference solution (a) to 25.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *styrene-divinylbenzene copolymer R* (8 µm) with a pore size of 100 nm;
– *temperature*: 55 °C.

Mobile phase: mixture prepared with *carbon dioxide-free water R* containing 52 g/L of *anhydrous sodium sulfate R*, 1.5 g/L of *sodium octanesulfonate R*, 3 mL/L of *tetrahydrofuran R* stabilised with *butylhydroxytoluene R*, and 50 mL/L of *0.2 M potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*. Degas.

Flow rate: 1.0 mL/min.

Post-column solution: *carbonate-free sodium hydroxide solution R* diluted 25-fold with *carbon dioxide-free water R*, which is added pulselessly to the column effluent using a 375 µL polymeric mixing coil.

Flow rate: 0.3 mL/min.

Detection: pulsed amperometric detector or equivalent with a gold working electrode, a silver-silver chloride reference electrode and a stainless steel auxiliary electrode which is the cell body, held at respectively + 0.05 V detection, + 0.75 V oxidation and – 0.15 V reduction potentials, with pulse durations according to the instrument used. The temperature of the detector is set at 35 °C.

NOTE: to prevent problems due to salt precipitation, the electrochemical cell can be flushed with water R overnight.