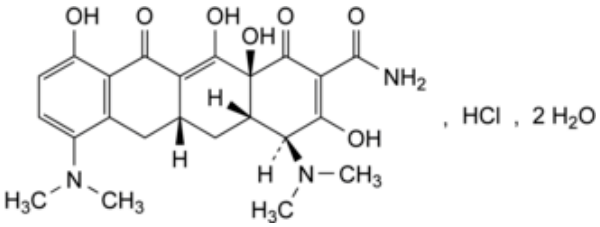
Edition: BP 2025 (Ph. Eur. 11.6 update)

Minocycline Hydrochloride Dihydrate

General Notices

Minocycline Hydrochloride

(Ph. Eur. monograph 1030)



$C_{23}H_{28}ClN_3O_7,2H_2O$ 530.0 *128420-71-3*

Action and use

Tetracycline antibacterial.

Preparations

Minocycline Capsules

Minocycline Prolonged-release Capsules

Minocycline Tablets

Ph Eur

DEFINITION

(4*S*,4a*S*,5a*R*,12a*S*)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride dihydrate.

Semi-synthetic product derived from a fermentation product.

Content

94.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow, hygroscopic, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *minocycline hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *minocycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *minocycline hydrochloride CRS* and 5 mg of *oxytetracycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase Mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a 63 g/L solution of *oxalic acid R* previously adjusted to pH 2 with *concentrated ammonia R*.

Application 1 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

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

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.200 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 450 nm using a 1 cm cell is not greater than 0.23.

Dilute 1.0 mL of solution S to 10.0 mL with *water R*.

pH (*2.2.3*)

3.5 to 4.5 for solution S.

Light-absorbing impurities

Carry out the measurement within 1 h of preparing solution S.

The absorbance (*2.2.25*) of solution S measured at 560 nm is not greater than 0.06.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light. Store the solutions at 2-8 °C and use them within 3 h of preparation.*

Solution A Mix 18 volumes of a 3.75 g/L solution of *sodium edetate R* and 60 volumes of a 28.3 g/L solution of *ammonium oxalate R* and adjust to pH 7.2 with *dilute ammonia R2*.

Test solution Dissolve 24.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 2 mg of *minocycline for system suitability CRS* (containing impurities A, B, C, E, F, G and H) in *water R* and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *tetrahydrofuran R*, *dimethylformamide R*, solution A (8:12:78 *V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time 3 times the retention time of minocycline.

Identification of impurities Use the chromatogram supplied with *minocycline for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, E, F, G and H.

Relative retention With reference to minocycline (retention time = about 16 min): impurity C = about 0.52; impurity H = about 0.55; impurity B = about 0.66; impurity A = about 0.74; impurity G = about 0.79; impurity F = about 0.92; impurity E = about 2.6.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities C and H; minimum 1.5 between the peaks due to impurities A and G; minimum 1.5 between the peaks due to impurity F and minocycline.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 1.6; impurity F = 1.6; impurity G = 1.4;

— for each impurity, use the concentration of minocycline hydrochloride dihydrate in reference solution (a).

Limits:

— *impurity A*: maximum 1.2 per cent;

— *impurity B*: maximum 0.8 per cent;

— *impurities C, E*: for each impurity, maximum 0.6 per cent;

— *impurities F, G*: for each impurity, maximum 0.5 per cent;

— *impurity H*: maximum 0.3 per cent;

— *any other impurity*: for each impurity, maximum 0.15 per cent;

— *total*: maximum 3.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

5.0 per cent to 8.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 1.25 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Test solution Dissolve 30.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution Dissolve 30.0 mg of *minocycline hydrochloride CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Injection Test solution and reference solution.

Calculate the percentage content of $C_{23}H_{28}ClN_3O_7$ taking into account the assigned content of *minocycline hydrochloride CRS*.

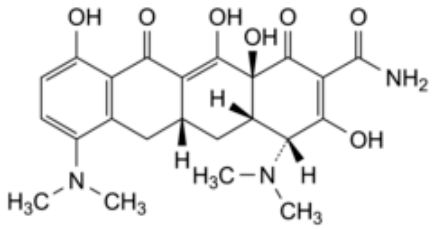
STORAGE

In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

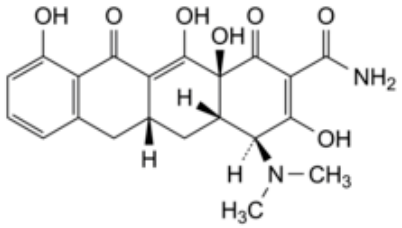
IMPURITIES

Specified impurities *A, B, C, E, F, G, H.*

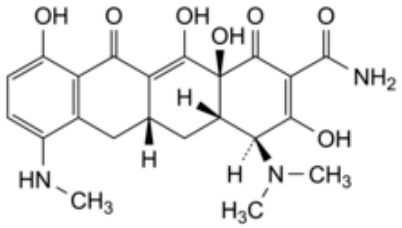
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for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



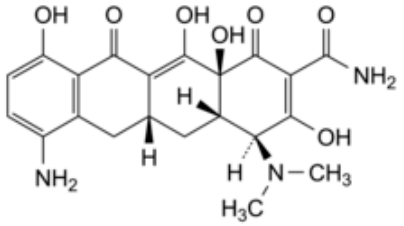
A. (4*R*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epiminocycline),



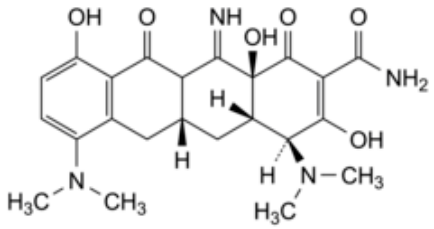
B. (4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (sancycline),



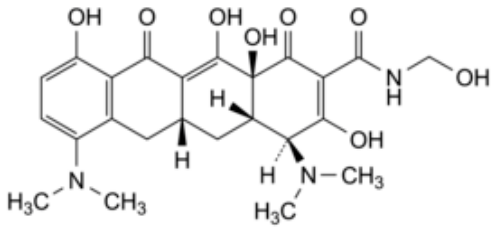
C. (4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-7-(methylamino)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (7-monodemethylminocycline),



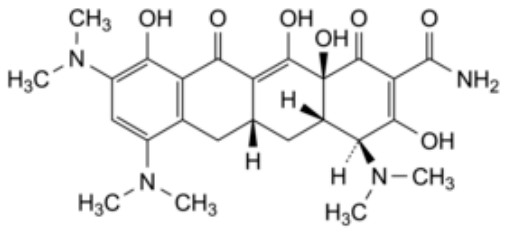
D. (4*S*,4a*S*,5a*R*,12a*S*)-7-amino-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (7-aminosancycline),



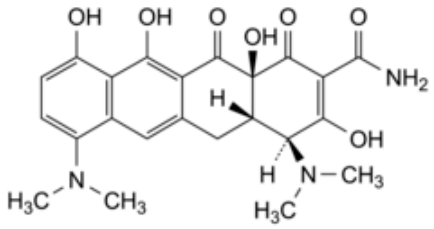
E. (4*S*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12a-trihydroxy-12-imino-1,11-dioxo-1,4,4a,5,5a,6,11,11a,12,12a-decahydrotetracene-2-carboxamide,



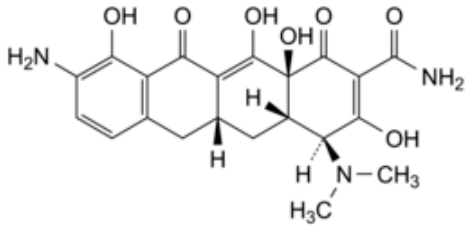
F. (4*S*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-*N*-(hydroxymethyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide,



G. (4*S*,4a*S*,5a*R*,12a*S*)-4,7,9-tris(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide,



H. (4*S*,4a*S*,12a*S*)-4,7-bis(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide,



I. (4*S*,4a*S*,5a*R*,12a*S*)-9-amino-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (9-aminosancycline).

Ph Eur