Minocycline Hydrochloride

Published on: 11.09.2023 **Last date for comments:** 10.11.2023

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

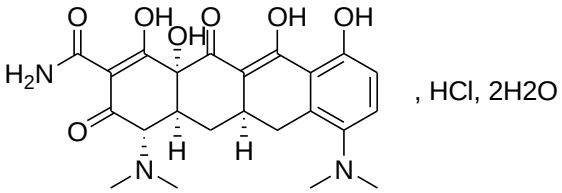
Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

Description	Details
Document version	1.0
Monograph proposed for inclusion	IP 2026
Tentative effective date of monograph	January, 2026
First draft published on IPC website for public comments	11.09.2023
Draft revision published on IPC website for public comments	-
Further follow-up action as required.	

Minocycline Hydrochloride

Minocycline Hydrochloride Dihydrate



, HCl, 2H2O

$C_{23}H_{28}ClN_3O_7,2H_2O$ Mol. Wt. 530.0

Minocycline Hydrochloride is semi-synthetic product derived from a fermentation product.

Minocycline Hydrochloride is (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.

Minocycline Hydrochloride contains not less than 94.5 per cent and not more than 102.0 per cent of $C_{23}H_{28}ClN_3O_7$ calculated on the anhydrous basis.

Category. Tetracycline antibiotics.

Description. A yellow, hygroscopic, crystalline powder.

Identification

Test B may be omitted if tests A and *C are carried out. Tests A may be omitted if test B* and *C is carried out*.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *minocycline Hydrochloride IPRS* or with the reference spectrum of minocycline Hydrochloride.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with silica gel GF254.

Mobile phase. A mixture of 60 volumes of a buffer solution prepared by dissolving 63 g of *oxalic acid* in 1000 ml of *water* adjusted to pH 2.0 with *concentrated ammonia*, 20 volumes of *acetonitrile* and 20 volumes of *methanol*.

Test solution. Dissolve 5 mg of the substance under examination in *methanol* and dilute to 10.0 ml with *methanol*.

Reference solution (a). A 0.05 per cent w/v solution of *minocycline hydrochloride IPRS* in *methanol*.

Reference solution (b). A solution containing 0.05 per cent w/v, each of, *minocycline hydrochloride IPRS* and *oxytetracycline hydrochloride IPRS* in *methanol*.

Apply to the plate 1 µl of each solution. Allow the mobile phase to rise over ¾ of the plate. After development, dry the plate in a current of air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

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

Tests

Solution A. A 1.0 per cent w/v solution in *carbon dioxide free water.*

Appearance of solution. Dilute 1.0 ml of solution A to 10.0 ml with *water*. The solution is clear (2.4.1) and its absorbance at 450 nm (2.4.7), using a 1 cm cell is not more than 0.23.

pH (2.4 24). 3.5 to 4.5, determined in solution A.

Light-absorbing impurities. The Absorbance of solution A at about 560 nm, (2.4.7) is not more than 0.06. *[Note – Carry out the measurement with in 1 hour of preparing solution A]*

Related substances. Determine by liquid chromatography (2.4.14).

NOTE —Carry out the test protected from light. Store the solution at 2° to 8° and Use within 3 hours of preparation.

Buffer solution. Mix 18 volumes of 0.38 per cent w/v solution of *sodium edetate* and 60 volumes of a 0.28 per cent w/v solution of *ammonium oxalate*, adjusted to pH 7.2 with *dilute ammonia.*

Test solution. Dissolve 24 mg of the substance under examination in *water* and dilute to 100.0 ml with *water*.

Reference solution (a). A 0.00024 per cent w/v solution of *minocycline hydrochloride IPRS* in *water*.

Reference solution (b). Dissolve 2 mg of *minocycline for system suitability IPRS* (Containing A, B, C, E, F, G and H) in *water* and dilute to 5.0 ml with *water*.

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with base-deactivated, end-capped octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40º,
- mobile phase: a mixture of 78 volumes of the buffer solution, 12 volumes of *dimethylformamide* and 8 volumes of *tetrahydrofuran*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Name	Relative retention time	Correction factor
Minocycline impurity C[1]	0.52	--
Minocycline impurity H[2]	0.55	--
Minocycline impurity B[3]	0.66	--
Minocycline impurity A[4]	0.74	--
Minocycline impurity G[5]	0.79	1.4
Minocycline impurity F[6]	0.92	1.6
Minocycline hydrochloride (Retention time: about 16 minutes)	1.0	--
Minocycline impurity E[7]	2.6	1.6

[1](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),
[2](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,
[3](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),
[4](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),
[5](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,
[6](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,
[7](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,

Inject reference solution (b) to identify the peaks due to minocycline impurity A, B, C, E, F, G and H.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to minocycline impurity C and minocycline impurity H is not less than 1.5, between the peaks due to minocycline impurity A and minocycline impurity G is not less than 1.5 and between the peaks due to minocycline impurity F and minocycline is not less than 1.5.

Inject reference solution (a) and the test solution. Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to minocycline impurity A is not more than 1.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.2 per cent), the area of any

peak corresponding to minocycline impurity B is not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent), the area of any peak corresponding minocycline impurity C and minocycline impurity E, each of, is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent), the area of any peak corresponding minocycline impurity F and minocycline impurity G, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any peak corresponding to minocycline impurity H is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any other secondary peak is not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent) and the sum of areas of all the secondary peaks is not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.5 per cent).Ignore any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulphated ash (2.3.18). Not more than 0.5 per cent.

Water (2.3.43). 5.0 per cent to 8.0 per cent, determined on 0.20 g.

Assay. Determine by liquid chromatography (2.4.14).

NOTE —Carry out the test protected from light. Store the solution at 2° to 8° and Use within 3 hours of preparation.

Test solution. Dissolve 30 mg of the substance under examination in *water* and dilute to 50.0 ml with *water*.

Reference solution. A 0.06 per cent w/v solution of *minocycline hydrochloride IPRS* in *water.*

Use chromatographic system as described under Related substances.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injection is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{23}H_{28}ClN_3O_7$.

Bacterial endotoxins (2.2.3). Not more than 1.25 Endotoxin unit per mg of minocycline hydrochloride.

Minocycline Hydrochloride intended for use in the manufacture of Parenteral Preparations without a further sterilization procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light and moisture, if the substance is sterile, the container is also sterile and tamper-evident.

Minocycline Hydrochloride:

Solubility: Sparingly soluble in *water*, slightly soluble in *ethanol (95 per cent)*. It dissolves in solution of alkali hydroxides and carbonates.