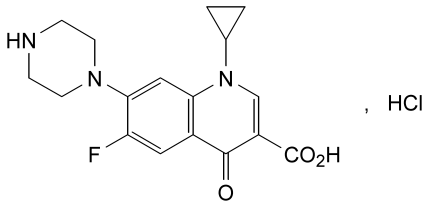
01/2008:0888

CIPROFLOXACIN HYDROCHLORIDE

Ciprofloxacini hydrochloridum



$C_{17}H_{19}ClFN_3O_3$ M_r 367.8
[86393-32-0]

DEFINITION

1-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.

Content: 98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: pale yellow, crystalline powder, slightly hygroscopic.

Solubility: soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, practically insoluble in acetone, in ethyl acetate and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Preparation: discs.
Comparison: *ciprofloxacin hydrochloride CRS*.

B. 0.1 g gives reaction (b) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 20 ml with the same solvent.

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution GY_5 (*2.2.2, Method II*).

Dilute 10 ml of solution S to 20 ml with *carbon dioxide-free water R*.

pH (*2.2.3*): 3.5 to 4.5 for solution S.

Impurity A. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 50 mg of the substance to be examined in *water R* and dilute to 5 ml with the same solvent.

Reference solution. Dissolve 10 mg of *ciprofloxacin impurity A CRS* in a mixture of 0.1 ml of *dilute ammonia R1* and 90 ml of *water R* and dilute to 100 ml with *water R*. Dilute 2 ml of the solution to 10 ml with *water R*.

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

Application: 5 µl.

At the bottom of a chromatographic tank, place an evaporating dish containing 50 ml of *concentrated ammonia R*. Expose the plate to the ammonia vapour for 15 min in the closed tank. Withdraw the plate, transfer to a second chromatographic tank and proceed with development.

Mobile phase: *acetonitrile R, concentrated ammonia R, methanol R, methylene chloride R* (10:20:40:40 *V/V/V/V*).

Development: over 3/4 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Limit:

– *impurity A*: any spot corresponding to impurity A is not more intense than the principal spot in the chromatogram obtained with the reference solution (0.2 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (a). Dissolve 25.0 mg of *ciprofloxacin hydrochloride CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (b). Dissolve 5 mg of *ciprofloxacin hydrochloride for peak identification CRS* in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (c). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 40 °C.

Mobile phase: mix 13 volumes of *acetonitrile R* and 87 volumes of a 2.45 g/l solution of *phosphoric acid R*, previously adjusted to pH 3.0 with *triethylamine R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 278 nm.

Injection: 50 µl.

Run time: twice the retention time of ciprofloxacin.

Relative retention with reference to ciprofloxacin (retention time = about 9 min): impurity E = about 0.4; impurity F = about 0.5; impurity B = about 0.6; impurity C = about 0.7; impurity D = about 1.2.

System suitability: reference solution (b):

– *resolution*: minimum 1.3 between the peaks due to impurity B and impurity C.

Limits:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.7; impurity C = 0.6; impurity D = 1.4; impurity E = 6.7; use the chromatogram obtained with reference solution (b) and the type chromatogram supplied with the CRS to identify the corresponding peaks;
– *impurities B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
– *any other impurity*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);
– *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);
– *disregard limit*: 0.25 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 20 ppm.

Dissolve 0.25 g in *water R* and dilute to 30 ml with the same solvent. Carry out the prefiltration. The filtrate complies with limit test E. Prepare the standard using 5 ml of *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*): maximum 6.7 per cent, determined on 0.200 g.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

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

Injection: 10 µl; inject the test solution and reference solution (a).

Calculate the percentage content of $C_{17}H_{19}ClFN_3O_3$.

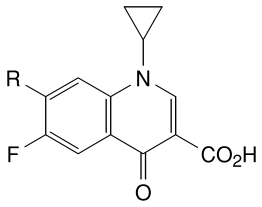
STORAGE

In an airtight container, protected from light.

IMPURITIES

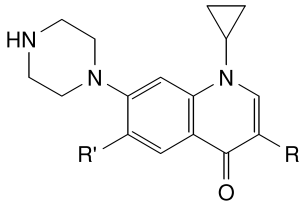
Specified impurities: A, B, C, D, E.

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*): *F.*



A. R = Cl: 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (fluoroquinolonic acid),

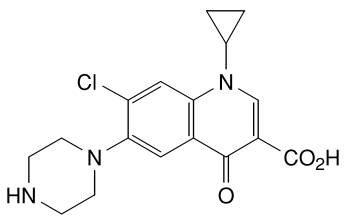
C. R = NH-[CH_2]$_2$-NH_2: 7-[(2-aminoethyl)amino]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (ethylenediamine compound),



B. R = CO_2H, R′ = H: 1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (desfluoro compound),

E. R = H, R′ = F: 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1*H*)-one (decarboxylated compound),

F. R = CO_2H, R′ = OH: 1-cyclopropyl-6-hydroxy-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,

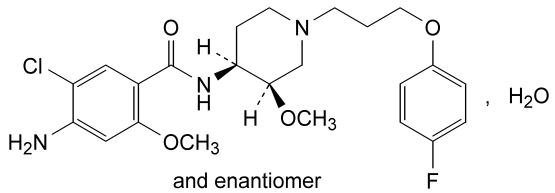


D. 7-chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

01/2008:0995

CISAPRIDE MONOHYDRATE

Cisapridum monohydricum



$C_{23}H_{29}ClFN_3O_4,H_2O$ M_r 484.0

DEFINITION

4-Amino-5-chloro-*N*-[(3*RS*,4*SR*)-1-[3-(4-fluorophenoxy)-propyl]-3-methoxypiperidin-4-yl]-2-methoxybenzamide monohydrate.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in dimethylformamide, soluble in methylene chloride, sparingly soluble in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *cisapride monohydrate CRS.*

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methanol R*, evaporate to dryness in a current of air and record new spectra using the residues.

TESTS

Solution S. Dissolve 0.20 g in *methylene chloride R* and dilute to 20.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Optical rotation (*2.2.7*): − 0.1° to + 0.1°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dissolve 5.0 mg of *cisapride monohydrate CRS* and 40.0 mg of *haloperidol CRS* in *methanol R* and dilute to 100.0 ml with the same solvent.

Reference solution (b). Dilute 5.0 ml of the test solution to 100.0 ml with *methanol R*. Dilute 1.0 ml of this solution to 10.0 ml with *methanol R*.

Column:

– *size*: *l* = 0.1 m, Ø = 4.0 mm;
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

– *mobile phase A*: 20 g/l solution of *tetrabutylammonium hydrogen sulphate R*;
– *mobile phase B*: *methanol R*;