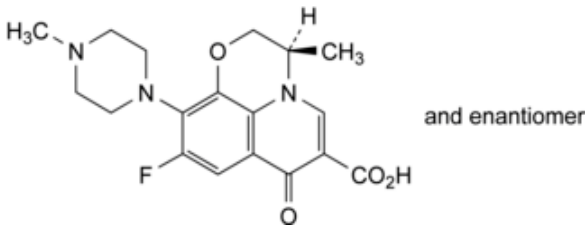
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ofloxacin

General Notices

(Ph. Eur. monograph 1455)



$C_{18}H_{20}FN_3O_4$ 361.4 *82419-36-1*

Action and use

Fluoroquinolone antibacterial.

Preparations

Ofloxacin Eye Drops

Ofloxacin Infusion

Ofloxacin Tablets

Ph Eur

DEFINITION

(3*RS*)-9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow or bright yellow, crystalline powder.

Solubility

Slightly soluble in water, soluble in glacial acetic acid, soluble or slightly soluble in methylene chloride, slightly soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ofloxacin CRS*.

B. Optical rotation (see Tests).

TESTS

Optical rotation (*2.2.7*)

-0.10° to + 0.10°.

Dissolve 0.300 g in a mixture of 10 volumes of *methanol R* and 40 volumes of *methylene chloride R* and dilute to 10.0 mL with the same mixture of solvents.

Absorbance (*2.2.25*)

Maximum 0.25 at 440 nm.

Dissolve 0.5 g in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solution.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (10:60 *V/V*).

Buffer solution Dissolve 3.08 g of *ammonium acetate R* and 5.38 g of *sodium perchlorate R* in about 900 mL of *water for chromatography R*. Adjust to pH 2.2 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5.0 mg of *levofloxacin impurity F CRS* (ofloxacin impurity A; *S*-enantiomer) in 42 mL of *acetonitrile R* and dilute to 250.0 mL with *water R*. Dilute 1.0 mL of this solution to 25.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *ofloxacin impurity D CRS* and 5 mg of *ofloxacin impurity E CRS* in the solvent mixture and dilute to 25 mL with the solvent mixture. Mix 2 mL of the solution and 1 mL of the test solution and dilute to 50 mL with the solvent mixture. Dilute 1 mL of this solution to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 38 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, buffer solution (16:84 *V/V*);

— *mobile phase B*: *methanol R1*, *acetonitrile for chromatography R*, buffer solution (20:30:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 10	100 → 82	0 → 18
10 - 15	82 → 40	18 → 60
15 - 30	40	60

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 294 nm and, for impurity A, at 240 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and E.

Relative retention With reference to ofloxacin (retention time = about 10 min): impurity D = about 0.7; impurity E = about 0.93; impurity A = about 2.8.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity E and ofloxacin in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 90 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 4.5;

— for impurity A, use the concentration of impurity A in reference solution (b) and the peak areas recorded at 240 nm;

— for impurities other than A, use the concentration of ofloxacin in reference solution (a) and the peak areas recorded at 294 nm.

Limits:

— *impurity A*: maximum 0.2 per cent;

— *impurity D*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.2 per cent, determined on 1.000 g by drying at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 100 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 36.14 mg of $C_{18}H_{20}FN_3O_4$.

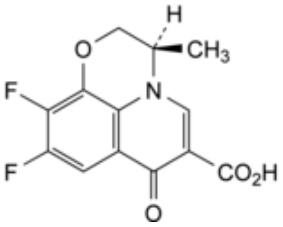
STORAGE

In an airtight container, protected from light.

IMPURITIES

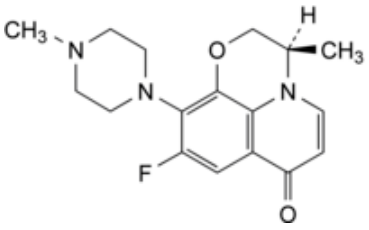
Specified impurities *A, D.*

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, C, E, F.*



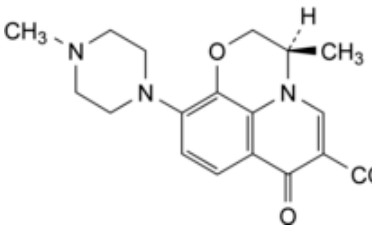
and enantiomer

A. (*3RS*)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid,



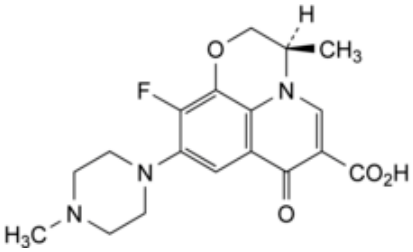
and enantiomer

B. (3*RS*)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-7-one,



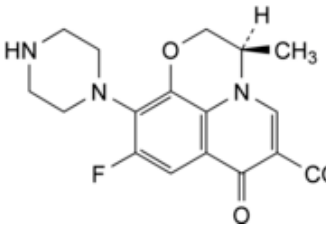
and enantiomer

C. (3*RS*)-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid,



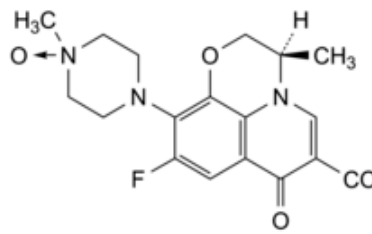
and enantiomer

D. (3*RS*)-10-fluoro-3-methyl-9-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid,



and enantiomer

E. (3*RS*)-9-fluoro-3-methyl-7-oxo-10-(piperazin-1-yl)-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid,



and enantiomer

F. 4-[(3*RS*)-6-carboxy-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-10-yl]-1-methylpiperazine 1-oxide.