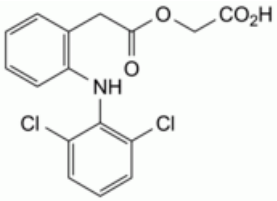
Edition: BP 2025 (Ph. Eur. 11.6 update)

Aceclofenac

General Notices

(Ph. Eur. monograph 1281)



$C_{16}H_{13}Cl_2NO_4$ 354.2 *89796-99-6*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

[[[2-[(2,6-Dichlorophenyl)amino]phenyl]acetyl]oxy]acetic acid.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in methanol R and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 50.0 mL with methanol R.

Spectral range 220-370 nm.

Absorption maximum 275 nm.

Specific absorbance at the absorption maximum 320 to 350.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison: Ph. Eur. reference spectrum of aceclofenac.

C. Dissolve about 10 mg in 10 mL of ethanol (96 per cent) R. To 1 mL of the solution, add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of potassium ferricyanide R and a 9 g/L solution of ferric chloride R. Allow to stand protected from light for 5 min. Add 3 mL of a 10.0 g/L solution of hydrochloric acid R. Allow to stand protected from light for 15 min. A blue colour develops and a precipitate is formed.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture Mobile phase A, mobile phase B (30:70 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 21.6 mg of diclofenac sodium CRS (impurity A) in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 2.0 mL of the test solution to 10.0 mL with the solvent mixture.

Reference solution (c) Mix 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) and dilute to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 4.0 mg of aceclofenac impurity F CRS in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (e) Dissolve 2.0 mg of aceclofenac impurity H CRS in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (f) Mix 1.0 mL of reference solution (b), 1.0 mL of reference solution (d) and 1.0 mL of reference solution (e) and dilute to 100.0 mL with the solvent mixture.

Reference solution (g) Dissolve 5.0 mg of aceclofenac impurity I CRS in the solvent mixture and dilute to 50.0 mL with solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (h) Dissolve 4 mg of aceclofenac for peak identification CRS (containing impurities B, C, D, E and G) in 2 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical end-capped octadecylsilyl silica gel for chromatography R (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent;

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1.12 g/L solution of phosphoric acid R adjusted to pH 7.0 with a 42 g/L solution of sodium hydroxide R;

— *mobile phase B*: *water R*, *acetonitrile R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	70 → 50	30 → 50
25 - 30	50 → 20	50 → 80
30 - 50	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL of the test solution and reference solutions (c), (d), (e), (f), (g) and (h).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram supplied with *aceclofenac for peak identification CRS* and the chromatogram obtained with reference solution (h) to identify the peaks due to impurities B, C, D, E and G; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity H; use the chromatogram obtained with reference solution (g) to identify the peak due to impurity I.

Relative retention With reference to aceclofenac (retention time = about 11 min): impurity A = about 0.8; impurity G = about 1.3; impurity H = about 1.5; impurity I = about 2.3; impurity D = about 3.1; impurity B = about 3.2; impurity E = about 3.3; impurity C = about 3.5; impurity F = about 3.7.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity A and aceclofenac.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurities B, C, D, E, G*: for each impurity, not more than the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.2 per cent);

— *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.2 per cent);

— *impurity H*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.15 per cent);

— *impurity I*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (g) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.10 per cent);

— *total*: maximum 0.7 per cent;

— *disregard limit*: 0.25 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 40 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

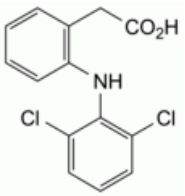
1 mL of *0.1 M sodium hydroxide* is equivalent to 35.42 mg of $C_{16}H_{13}Cl_2NO_4$.

STORAGE

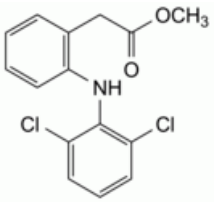
Protected from light.

IMPURITIES

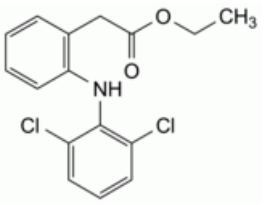
Specified impurities *A, B, C, D, E, F, G, H, I.*



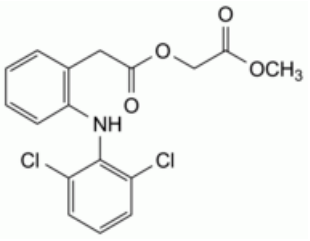
A. [2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid (diclofenac),



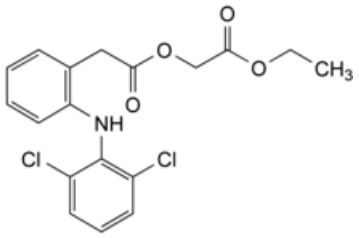
B. methyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (methyl ester of diclofenac),



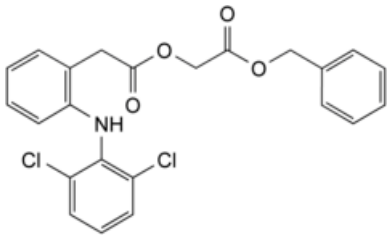
C. ethyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (ethyl ester of diclofenac),



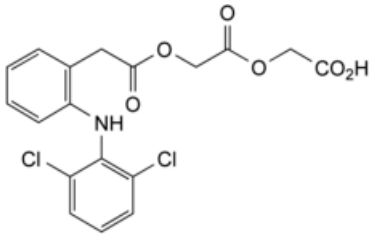
D. methyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (methyl ester of aceclofenac),



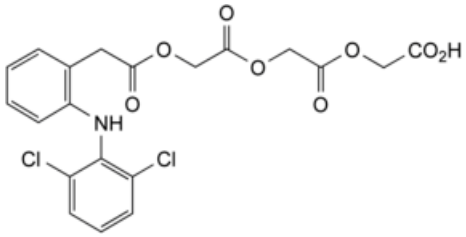
E. ethyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (ethyl ester of aceclofenac),



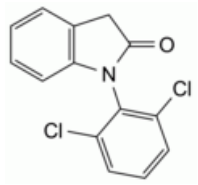
F. benzyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (benzyl ester of aceclofenac),



G. [[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac),



H. [[[[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetyl]oxy]acetic acid (diacetic aceclofenac),



I. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one.

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