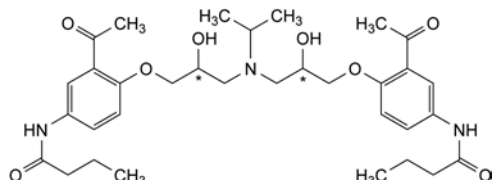
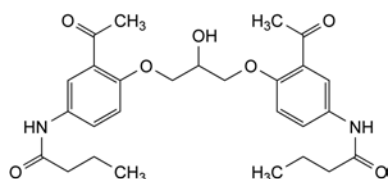


F. R = OH: *N*-[3-acetyl-4-[(2*RS*)-2,3-dihydroxypropoxy]phenyl]butanamide,

I. R = NH-CH₂-CH₃: *N*-[3-acetyl-4-[(2*RS*)-3-(ethylamino)-2-hydroxypropoxy]phenyl]butanamide,



G. *N,N'*-[[[(1-methylethyl)imino]bis[(2-hydroxypropane-1,3-diyl)oxy(3-acetyl-1,4-phenylene)]]dibutanamide (biamine),

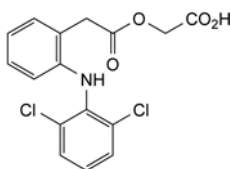


H. *N,N'*-[(2-hydroxypropane-1,3-diyl)bis[oxy(3-acetyl-1,4-phenylene)]]dibutanamide.

07/2009:1281

ACECLOFENAC

Aceclofenacum



C₁₆H₁₃Cl₂NO₄
[89796-99-6]

*M*_r 354.2

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. 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*. Examined between 220 nm and 370 nm (2.2.25), the solution shows an absorption maximum at 275 nm. The specific absorbance at the absorption maximum is 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.*

Test solution. Dissolve 50.0 mg of the substance to be examined in a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B and dilute to 25.0 mL with the same mixture of solvents.

Reference solution (a). Dissolve 21.6 mg of *diclofenac sodium CRS* (impurity A) in a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (b). Dilute 2.0 mL of the test solution to 10.0 mL with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

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 a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Reference solution (d). Dissolve 4.0 mg of *aceclofenac impurity F CRS* and 2.0 mg of *aceclofenac impurity H CRS* in a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B then dilute to 10.0 mL with the same mixture of solvents.

Reference solution (e). Mix 1.0 mL of reference solution (b) and 1.0 mL of reference solution (d) and dilute to 100.0 mL with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Reference solution (f). Dissolve the contents of a vial of *diclofenac impurity A CRS* (aceclofenac impurity I) in 1.0 mL of a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B, add 1.5 mL of the same mixture of solvents and mix.

Reference solution (g). Dissolve 4 mg of *aceclofenac for peak identification CRS* (containing impurities B, C, D, E and G) in 2.0 mL of a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

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 using a 42 g/L solution of *sodium hydroxide R*;
- *mobile phase B*: *water R*, *acetonitrile R* (1:9 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), (e), (f) and (g).

Identification of impurities: use the chromatogram supplied with *aceclofenac for peak identification CRS* and the chromatogram obtained with reference solution (g) to identify the peaks due to impurities B, C, D, E and G.

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 (e) (0.2 per cent);
- **impurity F:** not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.2 per cent);
- **impurity H:** not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.1 per cent);
- **impurity I:** not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.1 per cent);
- **unspecified impurities:** not more than 0.5 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (e) (0.10 per cent);
- **total:** not more than 0.7 per cent;
- **disregard limit:** 0.1 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (e) (0.02 per cent).

Heavy metals (2.4.8): maximum 10 ppm.

To 2.0 g in a silica crucible, add 2 mL of *sulfuric acid R* to wet the substance. Heat progressively to ignition and continue heating until an almost white or at most a greyish residue is obtained. Carry out the ignition at a temperature not exceeding 800 °C. Allow to cool. Add 3 mL of *hydrochloric acid R* and 1 mL of *nitric acid R*. Heat and evaporate slowly to dryness. Cool and add 1 mL of a 100 g/L solution of *hydrochloric acid R* and 10.0 mL of *distilled water R*. Neutralise with a 1.0 g/L solution of *ammonia R* using 0.1 mL of *phenolphthalein solution R* as indicator. Add 2.0 mL of a 60 g/L solution of *anhydrous acetic acid R* and dilute to 20 mL with *distilled water R*. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

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).

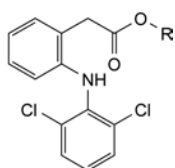
1 mL of 0.1 M *sodium hydroxide* is equivalent to 35.42 mg of $C_{16}H_{13}Cl_2NO_4$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

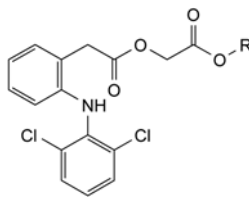
Specified impurities: A, B, C, D, E, F, G, H, I.



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

B. R = CH₃: methyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (methyl ester of diclofenac),

C. R = C₂H₅: ethyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (ethyl ester of diclofenac),



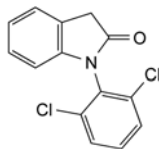
D. R = CH₃: methyl [[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (methyl ester of aceclofenac),

E. R = C₂H₅: ethyl [[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (ethyl ester of aceclofenac),

F. R = CH₂-C₆H₅: benzyl [[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (benzyl ester of aceclofenac),

G. R = CH₂-CO₂H: [[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac),

H. R = CH₂-CO-O-CH₂-CO₂H: [[[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetyl]oxy]acetic acid (diacetic aceclofenac),

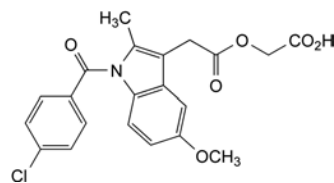


I. 1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one.

04/2008:1686
corrected 7.0

ACEMETACIN

Acemetacinum



$C_{21}H_{18}ClNO_6$
[53164-05-9]

M_r 415.8

DEFINITION

[[[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl]oxy]acetic acid.

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

CHARACTERS

Appearance: yellow or greenish-yellow, crystalline powder.

Solubility: practically insoluble in water, soluble in acetone, slightly soluble in anhydrous ethanol.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison: acemetacin CRS.