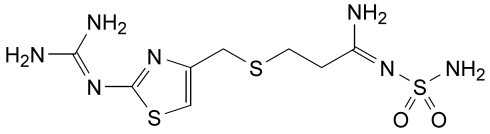
01/2008:1012

FAMOTIDINE

Famotidinum



$C_8H_{15}N_7O_2S_3$ M_r 337.5
[76824-35-6]

DEFINITION

3-[[[2-[(Diaminomethylene)amino]thiazol-4-yl]methyl]sulphanyl]-*N*′-sulphamoylpropanimidamide.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or yellowish-white, crystalline powder or crystals.

Solubility: very slightly soluble in water, freely soluble in glacial acetic acid, very slightly soluble in anhydrous ethanol, practically insoluble in ethyl acetate. It dissolves in dilute mineral acids.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *famotidine CRS*.

If the spectra obtained show differences, suspend 0.10 g of the substance to be examined and 0.10 g of the reference substance separately in 5 ml of *water R*. Heat to boiling and allow to cool, scratching the wall of the tube with a glass rod to initiate crystallisation. Filter, wash the crystals with 2 ml of iced *water R* and dry in an oven at 80 °C at a pressure not exceeding 670 Pa for 1 h. Record new spectra using the residues.

TESTS

Appearance of solution. Dissolve 0.20 g in a 50 g/l solution of *hydrochloric acid R*, heating to 40 °C if necessary, and dilute to 20 ml with the same acid. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 12.5 mg of the substance to be examined in mobile phase A and dilute to 25.0 ml with mobile phase A.

Reference solution (a). Dilute 1.0 ml of the test solution to 10.0 ml with mobile phase A. Dilute 1.0 ml of this solution to 100.0 ml with mobile phase A.

Reference solution (b). Dissolve 2.5 mg of *famotidine impurity D CRS* in *methanol R* and dilute to 10.0 ml with the same solvent. To 1.0 ml of the solution add 0.50 ml of the test solution and dilute to 100.0 ml with mobile phase A.

Reference solution (c). Dissolve 5.0 mg of *famotidine for system suitability CRS* (famotidine containing impurities A, B, C, D, E, F, G) in mobile phase A and dilute to 10.0 ml with mobile phase A.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm),
– *temperature*: 50 °C.

Mobile phase:

– *mobile phase A*: mix 6 volumes of *methanol R*, 94 volumes of *acetonitrile R* and 900 volumes of a 1.882 g/l solution of *sodium hexanesulphonate R* previously adjusted to pH 3.5 with *acetic acid R*,
– *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (ml/min)
0 - 23	100 → 96	0 → 4	1
23 - 27	96	4	1 → 2
27 - 47	96 → 78	4 → 22	2
47 - 48	78 → 100	22 → 0	2
48 - 54	100	0	2 → 1

Detection: spectrophotometer at 265 nm.

Injection: 20 µl.

Relative retention with reference to famotidine (retention time = about 21 min): impurity D = about 1.1; impurity C = about 1.2; impurity G = about 1.4; impurity F = about 1.5; impurity A = about 1.6; impurity B = about 2.0; impurity E = about 2.1.

System suitability:

– the chromatogram obtained with reference solution (c) is similar to the chromatogram supplied with *famotidine for system suitability CRS*;
– *retention time*: famotidine = 19-23 min in all the chromatograms; impurity E = maximum 48 min in the chromatogram obtained with reference solution (c);
– *resolution*: minimum 3.5 between the peaks due to famotidine and impurity D in the chromatogram obtained with reference solution (b).

Limits:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.9; impurity B = 2.5; impurity C = 1.9; impurity F = 1.7; impurity G = 1.4;
– *impurities A, G*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *impurities B, C, D, E*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), and not more than 3 such peaks have an area greater than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) for the peaks eluting by 25 min, and not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) for the peaks eluting after 25 min (0.1 per cent);
– *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);
– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a).

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with limit test D. Prepare the reference solution using 2 ml of *lead standard solution (10 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 80 °C at a pressure not exceeding 670 Pa for 5 h.

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

ASSAY

Dissolve 0.120 g in 60 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

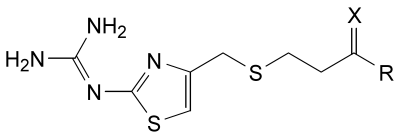
1 ml of *0.1 M perchloric acid* is equivalent to 16.87 mg of $C_8H_{15}N_7O_2S_3$.

STORAGE

Protected from light.

IMPURITIES

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



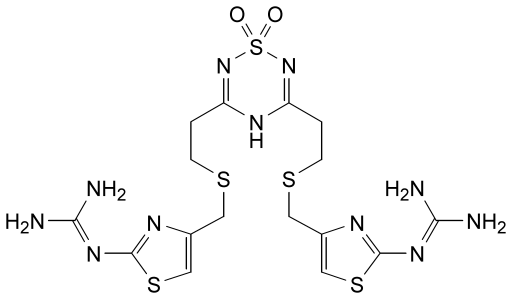
A. R = NH_2, X = NH: 3-[[[2-[(diaminomethylene)amino]thiazol-4-yl]methyl]sulphanyl]propanimidamide,

C. R = NH-SO_2-NH_2, X = O: 3-[[[2-[(diaminomethylene)amino]thiazol-4-yl]methyl]sulphanyl]-*N*-sulphamoylpropanamide,

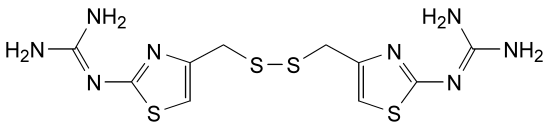
D. R = NH_2, X = O: 3-[[[2-[(diaminomethylene)amino]thiazol-4-yl]methyl]sulphanyl]propanamide,

F. R = OH, X = O: 3-[[[2-[(diaminomethylene)amino]thiazol-4-yl]methyl]sulphanyl]propanoic acid,

G. R = NH-CN, X = NH: *N*-cyano-3-[[[2-[(diaminomethylene)amino]thiazol-4-yl]methyl]sulphanyl]propanimidamide,



B. 3,5-bis[2-[[[2-[(diaminomethylene)amino]thiazol-4-yl]methyl]sulphanyl]ethyl]-4*H*-1,2,4,6-thiatriazine 1,1-dioxide,

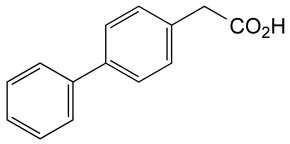


E. 2,2′-[disulphanediylbis(methylenethiazole-4,2-diyl)]diguanidine.

01/2008:2304

FELBINAC

Felbinacum



$C_{14}H_{12}O_2$ M_r 212.2

[5728-52-9]

DEFINITION

(Biphenyl-4-yl)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, soluble in methanol, sparingly soluble in ethanol (96 per cent).

mp: about 164 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *felbinac CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Protect the solutions from light and inject within 20 min of preparation.*

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. Dissolve 5.0 mg of *felbinac impurity A CRS* and 5.0 mg of *biphenyl R* (impurity B) in *methanol R*, add 0.5 ml of the test solution and dilute to 50.0 ml with *methanol R*. Dilute 1.0 ml of this solution to 10.0 ml with *methanol R*.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 45 volumes of a 0.1 per cent *V/V* solution of *glacial acetic acid R* and 55 volumes of *methanol R*.

Flow rate: 2 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µl.

Run time: 3.5 times the retention time of felbinac.

Relative retention with reference to felbinac (retention time = about 15 min): impurity A = about 1.3; impurity B = about 2.8.

System suitability: reference solution:

– *resolution*: minimum 3.0 between the peaks due to felbinac and impurity A.

Limits:

– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent);