E. (3aS,4R,6S,8R,9R,9aR,10R)-6-ethenyl-4,6,9,10-tetramethyl-5-dihydroxy-3a,9-propano-3aH-cyclopentacycloocten-8-yl [[2-(diethylamino)ethyl]sulphanyl]acetate (11-oxotiamulin),

F. (1RS,3aR,4S,6S,8R,9R,9aR,10R)-6-ethenyl-1-hydroxy-4,6,9,10-tetramethyl-5-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl [[2-(diethylamino)ethyl]sulphanyl]acetate (1-hydroxy-11-oxotiamulin),


I. (2E)-4-[[3aS,4R,5S,6S,8R,9R,9aR,10R]-8-[[2-(diethylamino)ethyl]sulphanyl]acetyl]oxy]-6-ethenyl-1,5-dihydroxy-4,6,9,10-tetramethyldecahydro-3a,9-propano-3aH-cyclopentacycloocten-2-yl[oxyl]4-oxobut-2-enoic acid (2,3-dihydroxytiamulin 2-fumarate),

N. (2E)-4-[[3aS,4R,5S,6S,8R,9R,9aR,10R]-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl[oxyl]2-oxoethoxy]-4-oxobut-2-enoic acid (pleuromutilin 22-fumarate),

Q. (3aS,4R,5S,6S,8R,9R,10R)-6-ethenyl-2,5-dihydroxy-4,6,9,10-tetramethyl-2,3,4,5,6,7,8,9-octahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl [[2-(diethylamino)ethyl]sulphanyl]acetate (3,4-didehydro-2-hydroxytiamulin),

R. N-benzyl-N,N-dibutylbutan-1-aminium.

TIAMULIN HYDROGEN FUMARATE
FOR VETERINARY USE

Tiamulini hydrogenofumaras ad usum veterinarium

C₃₂H₅₁NO₈S

Mₙ, 610

DEFINITION
(3aS,4R,5S,6S,8R,9R,9aR,10R)-6-Ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl [[2-(diethylamino)ethyl]sulphanyl]acetate hydrogen (E)-but-2-enedioate.
Content: 96.5 per cent to 102.0 per cent (dried substance).

CHARACTERS
Appearance: white or light yellow, crystalline powder.
Solubility: soluble in water, freely soluble in anhydrous ethanol and soluble in methanol.

IDENTIFICATION
Infrared absorption spectrophotometry (2.2.24).
Comparison: tiamulin hydrogen fumarate CRS.

TESTS
pH (2.2.3): 3.1 to 4.1.
Dissolve 0.5 g in carbon dioxide-free water R and dilute to 50 ml with the same solvent.

Related substances. Liquid chromatography (2.2.29).
Ammonium carbonate buffer solution pH 10.0. Dissolve 10.0 g of ammonium carbonate R in water R, add 22 ml of perchloric acid solution R and dilute to 1000.0 ml with water R. Adjust to pH 10.0 with concentrated ammonia R1.
Tiamulin hydrogen fumarate for veterinary use

Solvent mixture: ammonium carbonate buffer solution pH 10.0, acetonitrile R1 (50:50 V/V).

Test solution. Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). Dissolve 0.200 g of tiamulin hydrogen fumarate CRS in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with the solvent mixture.

Reference solution (c). Dissolve 40.0 mg of fumaric acid R in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (d). Dissolve 4 mg of tiamulin for peak identification CRS (tiamulin hydrogen fumarate containing impurities B, C, D, F, H and I) in the solvent mixture and dilute to 1 ml with the solvent mixture.

Column:
- size: i = 0.15 m, Ø = 4.6 mm,
- stationary phase: end-capped octadecysilyl silica gel for chromatography R (5 µm),
- temperature: 30 °C.


Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 212 nm.

Injection: 20 µl.

Run time: 3 times the retention time of tiamulin.

Identification of impurities: use the chromatogram supplied with tiamulin for peak identification CRS and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B and H.

Relative retention with reference to tiamulin (retention time = about 18 min): impurity G = about 0.2;
impurity A = about 0.22; impurity H = about 0.23;
impurity I = about 0.3; impurity J = about 0.4;
impurity K = about 0.45; impurity B = about 0.5;
impurity L = about 0.65; impurity C = about 0.66;
impurity F = about 0.8; impurity M = about 0.85;
impurity D = about 1.1; impurity S = about 1.4;
impurity T = about 1.6; impurity E = about 2.4.

System suitability: reference solution (a):
- baseline separation between the peaks due to tiamulin and impurity D.

Limits:
- impurities B, H: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent)
- impurities A, C, D, E, F, G, I, J, K, L, M, S, T: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent)
- any other impurity: for each impurity, not more than 0.2 times the area of the peak of the principal impurity in the chromatogram obtained with reference solution (b) (0.2 per cent).
- total: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent).
- disregard limit: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent); disregard any peak present in reference solution (c).

Loss on drying (2.2.32): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 100-105 °C.

ASSAY

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

Injection: test solution and reference solution (a).

Calculate the percentage content of C32H51NO8S from the declared content of tiamulin hydrogen fumarate CRS.

STORAGE

Protected from light.

IMPURITIES


Other detectable impurities: N, O, P, Q, R.

A. R1 = R2 = H: (3aS,AR,5S,6S,8R,9R,9aR,10R)-6-ethenyl-5,8-dihydroxy-4,6,9,10-tetramethylloctahydro-3a,9-propano-3aH-cyclopentacycloocten-1(4H)-one (mutilin),

G. R1 = CO-CH2OH, R2 = H: (3aS,AR,5S,6S,8R,9R,9aR,10R)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl hydroxycacetate (pleuromutilin),

J. R1 = CO-CH3, R2 = H: (3aS,AR,5S,6S,8R,9R,9aR,10R)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-9-yl acetate (mutilin 14-acetate),

K. R1 = H, R2 = CO-CH3: (3aS,AR,5S,6S,8R,9R,9aR,10R)-6-ethenyl-8-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-5-yl acetate (mutilin 11-acetate),

L. R1 = CO-CH2-O-SO2-C6H5-pCH3, R2 = H: (3aS,AR,5S,6S,8R,9R,9aR,10R)-6-ethenyl-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl [[4-methylphenyl]sulphonyloxy]acetate (pleuromutilin 22-tosylate),

M. R1 = R2 = CO-CH3: (3aS,AR,5S,6S,8R,9R,9aR,10R)-6-ethenyl-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-5,8-diyl diacetate (mutilin 11,14-diacetate),

P. R1 = CO-CH2-O-SO2-C6H5-H, R2 = H: (3aS,AR,5S,6S,8R,9R,9aR,10R)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl [[phenylsulphonyloxy]acetate,

T. R1 = CO-CH2-[S(CH2CH2)3]N(C6H5)3, R2 = H: (3aS,AR,5S,6S,8R,9R,9aR,10R)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl [[2-[[2-(diethylamino)ethyl]sulphanilyl]ethyl]sulphanilyl]acetate,
**Tianeptine sodium**

**DEFINITION**

Sodium 7-[(11RS)-3-chloro-6-methyl-6,11-dihydrodibenzoc[\(\text{c},\text{f}\)]\[1,2\]thiazepin-11-yl]amino-2-ethoxyethoxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3aH-cyclopentacycloocten-8-yl][oxy]-2-oxoethoxy-4-oxobut-2-enoic acid (pleuromutilin 22-fumarate),

\[\text{C}_{21}\text{H}_{24}\text{ClN}_{2}\text{NaO}_{4}\text{S}\]

\[M_r 458.9\]

**DEFINITION**

Sodium 7-[(11RS)-3-chloro-6-methyl-6,11-dihydrodibenzo[\(c, f\)][1,2]thiazepin-11-yl]amino]heptanoate S,S-dioxide.

\[\text{C}_{13}\text{H}_{27}\text{ClN}_{2}\text{NaO}_{5}\]

\[M_r 458.9\]