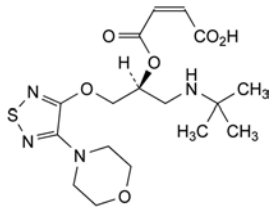
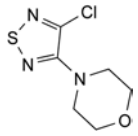
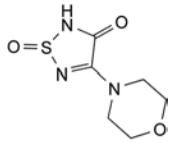


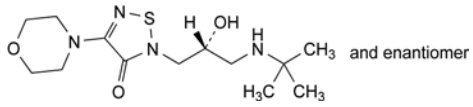
E. (2*Z*)-4-[(1*S*)-1-[[(1,1-dimethylethyl)amino]methyl]-2-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]ethoxy]-4-oxobut-2-enoic acid,



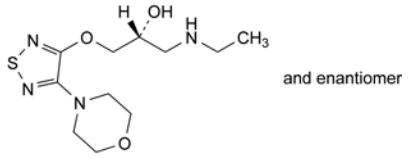
F. 4-(4-chloro-1,2,5-thiadiazol-3-yl)morpholine,



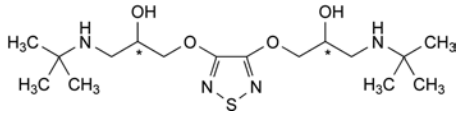
G. 4-(morpholin-4-yl)-1,2,5-thiadiazol-3(2*H*)-one 1-oxide,




H. 2-[(2*RS*)-3-[(1,1-dimethylethyl)amino]-2-hydroxypropyl]-4-(morpholin-4-yl)-1,2,5-thiadiazol-3(2*H*)-one,




I. (2*RS*)-1-(ethylamino)-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol,

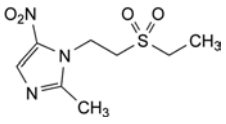


J. 1,1′-[1,2,5-thiadiazol-3,4-diylbis(oxy)]bis[3-[(1,1-dimethylethyl)amino]propan-2-ol].

**07/2008:1051**

# TINIDAZOLE

## Tinidazolum



$C_8H_{13}N_3O_4S$ $M_r$ 247.3
[19387-91-8]

DEFINITION

1-[2-(Ethylsulfonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole.

*Content*: 98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

*Appearance*: almost white or pale yellow, crystalline powder.

*Solubility*: practically insoluble in water, soluble in acetone and in methylene chloride, sparingly soluble in methanol.

IDENTIFICATION

*First identification*: *A, C.*

*Second identification*: *A, B, D, E.*

A. Melting point (*2.2.14*): 125 °C to 128 °C.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

*Test solution.* Dissolve 10.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

*Spectral range*: 220-350 nm.

*Absorption maximum*: at 310 nm.

*Specific absorbance at the absorption maximum*: 340 to 360.

C. Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *tinidazole CRS.*

D. Thin-layer chromatography (*2.2.27*).

*Test solution.* Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

*Reference solution.* Dissolve 20 mg of *tinidazole CRS* in *methanol R* and dilute to 10 mL with the same solvent.

*Plate*: *TLC silica gel* $GF_{254}$ *plate R.*

*Pretreatment*: heat at 110 °C for 1 h and allow to cool.

*Mobile phase*: *butanol R, ethyl acetate R* (25:75 *V/V*).

*Application*: 10 µL.

*Development*: over 2/3 of the plate.

*Drying*: in air.

*Detection*: examine in ultraviolet light at 254 nm.

*Results*: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

E. To about 10 mg add about 10 mg of *zinc powder R*, 0.3 mL of *hydrochloric acid R* and 1 mL of *water R*. Heat in a water-bath for 5 min and cool. The solution gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

**Appearance of solution**. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution $Y_5$ (*2.2.2, Method II*).

Dissolve 1.0 g in *acetone R* and dilute to 20 mL with the same solvent.

**Related substances**. Liquid chromatography (*2.2.29*). *Protect solutions from light.*

*Test solution.* Dissolve 10.0 mg of the substance to be examined in 10.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

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

*Reference solution (b).* Dissolve 5.0 mg of *tinidazole impurity A CRS* and 5.0 mg of *tinidazole impurity B CRS* in 10.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

*Reference solution (c).* Dilute 1.0 mL of reference solution (b) to 50.0 mL with the mobile phase.

*Column*:

– *size*: *l* = 0.25 m, Ø = 3.0 mm;
– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Regular column conditioning by subsequent flushing with 50 mL of *water R*, 100 mL of *methanol R*, 25 mL of *water R* and 100 mL of the mobile phase is recommended.

*Mobile phase*: *acetonitrile R, methanol R, water R* (10:20:70 *V/V/V*).

*Flow rate*: 0.5 mL/min.

*Detection*: spectrophotometer at 320 nm.

*Injection*: 20 µL.

*Run time*: 1.5 times the retention time of tinidazole.

*Relative retention* with reference to tinidazole (retention time = about 6 min): impurity A = about 0.6; impurity B = about 0.7.

*System suitability*: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to impurities A and B.

*Limits*:

– *impurities A, B*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

– *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

**Heavy metals** (*2.4.8*): maximum 20 ppm.

1.0 g complies with 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 105 °C.

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

ASSAY

Dissolve 0.150 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

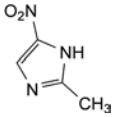
1 mL of *0.1 M perchloric acid* is equivalent to 24.73 mg of $C_8H_{13}N_3O_4S$.

STORAGE

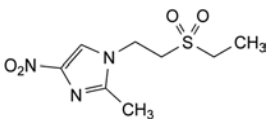
Protected from light.

IMPURITIES

*Specified impurities: A, B.*



A. 2-methyl-5-nitro-1*H*-imidazole,

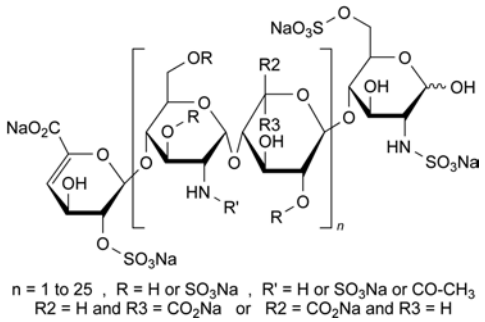


B. 1-[2-(ethylsulfonyl)ethyl]-2-methyl-4-nitro-1*H*-imidazole.

**01/2008:1271**

# TINZAPARIN SODIUM

## Tinzaparinum natricum




DEFINITION

Tinzaparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by controlled enzymatic depolymerisation of heparin from porcine intestinal mucosa using heparinase from *Flavobacterium heparinum*. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain.

*Tinzaparin sodium complies with the monograph on Low-molecular-mass heparins (0828) with the modifications and additional requirements below.*

The mass-average relative molecular mass ranges between 5500 and 7500 with a characteristic value of about 6500.

The degree of sulfatation is 1.8 to 2.5 per disaccharide unit.

The potency is not less than 70 IU and not more than 120 IU of anti-factor Xa activity per milligram calculated with reference to the dried substance. The ratio of the anti-factor Xa activity to anti-factor IIa activity is between 1.5 and 2.5.

IDENTIFICATION

Carry out identification test A as described in the monograph for *Low-molecular-mass heparins (0828)* using *tinzaparin sodium CRS*.

Carry out identification test C as described in the monograph for *Low-molecular-mass heparins (0828)*. The following requirements apply.

The mass-average relative molecular mass ranges between 5500 and 7500. The mass percentage of chains lower than 2000 is not more than 10.0 per cent. The mass percentage of chains between 2000 and 8000 ranges between 60.0 and 72.0 per cent. The mass percentage of chains above 8000 ranges between 22.0 and 36.0 per cent.

TESTS

**Appearance of solution**. Dissolve 1.0 g in 10 mL of *water R*. The solution is clear (*2.2.1*) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*)

**Absorbance** (*2.2.25*). Dissolve 50.0 mg in 100 mL of *0.01 M hydrochloric acid*. The specific absorbance, measured at 231 nm and calculated with reference to the dried substance, is 8.0 to 12.5.