$M_{r}$  350.9

# RANITIDINE HYDROCHLORIDE

# Ranitidini hydrochloridum

$$\begin{array}{c|c} H_3C \\ \hline \\ H_3C \\ \hline \\ O \\ S \\ \hline \\ N \\ H \\ H \\ N \\ CH_3 \\ \end{array}, \ \ HCI$$

 $C_{13}H_{23}ClN_4O_3S$ 

### **DEFINITION**

N-[2-[[[5-[(Dimethylamino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-N'-methyl-2-nitroethene-1,1-diamine hydrochloride.

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

#### **CHARACTERS**

Appearance: white or pale yellow, crystalline powder.

Solubility: freely soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, very slightly soluble in methylene chloride.

It shows polymorphism.

#### **IDENTIFICATION**

A. Infrared absorption spectrophotometry (2.2.24).

Comparison: ranitidine hydrochloride CRS.

If the spectra show differences, dissolve 10 mg of the substance to be examined and 10 mg of the reference substance separately in 0.5 ml of methanol R in an agate mortar. Evaporate to dryness under a stream of nitrogen R. Dry the residues under vacuum for 30 min. Add 3 drops of *liquid paraffin R* to the residues and triturate until the mull shows a milky appearance. Compress the mulls between 2 plates transparent to infrared radiation and record new spectra.

B. It gives reaction (a) of chlorides (2.3.1).

#### **TESTS**

**Solution S.** Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100.0 ml with the same solvent.

**Appearance of solution.** Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY<sub>5</sub> (2.2.2, Method II).

**pH** (2.2.3): 4.5 to 6.0 for solution S.

**Related substances.** Liquid chromatography (2.2.29).

Buffer solution. Dissolve 6.8 g of potassium dihydrogen phosphate R in 950 ml of water R. Adjust to pH 7.1 with strong sodium hydroxide solution R and dilute to 1000 ml with water R.

Test solution. Dissolve 13 mg of the substance to be examined in mobile phase A and dilute to 100 ml with mobile phase A.

Reference solution (a). Dissolve 6.5 mg of ranitidine for system suitability CRS (ranitidine with impurities A, D and H) in mobile phase A and dilute to 50 ml with mobile

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

**04/2005:0946** Reference solution (c). Dissolve the contents of a vial of ranitidine impurity J CRS in 2 ml of mobile phase A. Dilute 0.5 ml of the solution to 50 ml with mobile phase A. Dilute 1 ml of this solution to 20 ml with the test solution.

- size: l = 0.1 m,  $\emptyset = 4.6 \text{ mm}$ ,
- stationary phase: end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R
- temperature: 35 °C.

#### Mobile phase:

- mobile phase A: acetonitrile R, buffer solution (2:98 V/V),
- *mobile phase B: acetonitrile R*, buffer solution  $(22:78 \ V/V),$

Time (min)	Mobile phase A (per cent <i>V/V</i> )	Mobile phase B (per cent V/V)
0 - 10	$100 \rightarrow 0$	$0 \rightarrow 100$
10 - 15	0	100
15 - 16	$0 \rightarrow 100$	$100 \rightarrow 0$
16 - 20	100	0

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 230 nm.

*Injection*: 10 µl of the test solution, reference solutions (a), (b) and (c) and mobile phase A as a blank.

Relative retention with reference to ranitidine (retention

time = about 6.8 min): impurity H = about 0.1:

impurity G = about 0.2; impurity F = about 0.4; impurity B = about 0.5; impurity C = about 0.6;

impurity E = about 0.7; impurity D = about 0.8;

impurity J = about 0.9; impurity I = about 1.3;

impurity A = about 1.7.

## System suitability:

- resolution: minimum 1.5 between the peaks due to impurity J and ranitidine in the chromatogram obtained with reference solution (c),
- the chromatogram obtained with reference solution (a) is similar to the chromatogram supplied with *ranitidine* for system suitability CRS,
- the chromatogram obtained with the blank does not show any peak with the same relative retention as the peak due to impurity A in the chromatogram obtained with reference solution (a).

#### Limits:

- correction factor: for the calculation of content, multiply the peak area of impurity J by 2,
- impurity A: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),
- *impurities B, C, D, E, F, G, H, I, J*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),
- any other impurity: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- sum of impurities other than A: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),
- disregard limit: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to the blank.

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

1.0 g complies with limit test C. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

**Loss on drying** (2.2.32): maximum 0.75 per cent, determined on 1.000 g by drying under high vacuum at 60  $^{\circ}$ C.

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

#### **ASSAY**

Dissolve 0.280 g in 35 ml of *water 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 35.09 mg of  $C_{13}H_{23}ClN_4O_3S$ .

#### **STORAGE**

In airtight container, protected from light.

#### **IMPURITIES**

Specified impurities: A, B, C, D, E, F, G, H, I, J. Other detectable impurities: K.

$$H_3C$$
 $N-CH_3$ 
 $H_3C-N$ 
 $NO_2$ 
 $NO_$ 

A. *N,N*-bis[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-2-nitroethene-1,1-diamine,

- B.  $R = S-CH_2-CH_2-NH_2$ : 2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulphanyl]ethanamine,
- D. R = S-CH<sub>2</sub>-CH<sub>2</sub>-NH-CO-CH<sub>2</sub>-NO<sub>2</sub>: *N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-2-nitroacetamide,
- F. R = OH: [5-[(dimethylamino)methyl]furan-2-yl]methanol,

$$\begin{array}{c|c} H_3C \\ \hline \\ N \\ \hline \\ O \\ S \\ \hline \\ N \\ H \\ \end{array} \begin{array}{c} NO_2 \\ \\ N \\ CH_3 \\ \end{array}$$

C. *N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulphinyl]ethyl]-*N*'-methyl-2-nitroethene-1,1-diamine,

$$H_3C$$
 $O \leftarrow N$ 
 $H_3C$ 
 $O \rightarrow N$ 
 $NO_2$ 
 $NO_2$ 

E. *N*-[2-[[[5-[(dimethyloxidoamino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-*N*′-methyl-2-nitroethene-1,1-diamine.

G. 3-(methylamino)-5,6-dihydro-2*H*-1,4-thiazin-2-one-oxime,

H. N-methyl-2-nitroacetamide,

$$H_3C - N$$
 $O$ 
 $S$ 
 $H_3C$ 
 $CH_3$ 
 $CNO_2$ 
 $CH_2$ 
 $CNO_2$ 
 $CNO_2$ 
 $CH_3$ 
 $CNO_2$ 
 $CH_3$ 
 $CNO_2$ 
 $CH_3$ 
 $CNO_2$ 
 $CH_3$ 
 $CNO_2$ 
 $CH_3$ 
 $CNO_2$ 

I. 2,2'-methylenebis[N-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-N'-methyl-2-nitroethene-1,1-diamine],

$$H_3C$$
 $NO_2$ 
 $NO_2$ 

J. 1,1'-N-[methylenebis(sulphanediylethylene)]bis(N'-methyl-2-nitroethene-1,1-diamine),

K. *N*-methyl-1-methylthio-2-nitroethenamine.

01/2005:2109 corrected

## RIBAVIRIN

## Ribavirinum

 $C_8H_{12}N_4O_5$   $M_r 244.2$ 

# DEFINITION

1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide. *Content*: 98.0 per cent to 102.0 per cent (dried substance).

# CHARACTERS

Appearance: white or almost white, crystalline powder. Solubility: freely soluble in water, slightly soluble in ethanol (96 per cent), slightly soluble or very slightly soluble in methylene chloride.