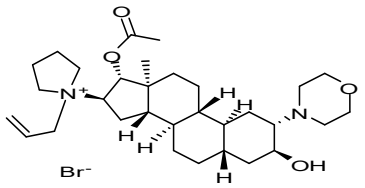
Rocuronium Bromide



$C_{32}H_{53}BrN_2O_4$ Mol. Wt. 609.7

Rocuronium Bromide is 1-[17β-Acetoxy-3α-hydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium bromide.

Rocuronium Bromide contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{32}H_{53}BrN_2O_4$, calculated on the anhydrous basis.

Category. Non-depolarizing neuromuscular blocker.

Description. Almost white or pale yellow, slightly hygroscopic powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *rocuronium bromide IPRS* or with the reference spectrum of rocuronium bromide.

B. A 1 per cent w/v solution in *carbon dioxide-free water* (solution A) gives reaction (a) of bromides (2.3.1).

Tests

Appearance of solution. Solution A is clear (2.4.1) and not more intensely coloured than reference solution BYS5 (2.4.1).

pH (2.4.24). 8.9 to 9.5, determined in solution A.

Specific optical rotation (2.4.22). +28.5° to +32.0°, determined in a 1 per cent w/v solution in *0.05 M hydrochloric acid*.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 10 volumes of *water* and 90 volumes of *acetonitrile.*

Test solution. Dissolve 100 mg of the substance under examination in the solvent mixture and dilute to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.001 per cent w/v solution of *rocuronium bromide IPRS* in the solvent mixture.

Reference solution (b). A 0.1 per cent w/v solution of *rocuronium for peak identification IPRS (containing impurities A, B, C, F, G and H)* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with porous silica (5 µm),
- mobile phase: a mixture of 10 volumes of buffer solution prepared by dissolving 4.53 g of *tetramethylammonium hydroxide* in 1000 ml of *water*, adjusted to pH 7.4 with *orthophosphoric acid* and 90 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 5 µl.

Name	Relative retention time	Correction factor
Rocuronium impurity A[1]	0.2	0.5
Rocuronium impurity G[2]	0.4	0.4
Rocuronium impurity F[3]	0.75	1.3
Rocuronium impurity B[4]	0.8	--
Rocuronium impurity H[5]	0.95	0.4
Rocuronium (retention time is about 9 minutes)	1.0	--
Rocuronium impurity C[6]	1.2	--

[1]3α-hydroxy-2β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstan-17β-yl acetate,
[2]β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstane-3α,17β-diol,
[3]1-[3α,17β-acetoxy-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,
[4]1-[3α,17β-diacetoxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,
[5]1-[17β-acetoxy-2-(morpholin-4-yl)-3-oxo-5α-androst-1-en-16β-yl]-1-(prop-2-enyl)pyrrolidinium,

[6]1-[3α,17β-dihydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

NOTE – Equilibrate the column at least for 4 hours.

Inject reference solution (b). The test is not valid unless the peak-to-valley ratio is not less than 3.0, where Hp is the height above the baseline of the peak due to impurity H and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to rocuronium.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to rocuronium impurity A, B, C, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to rocuronium impurity F, G, H, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak eluting before impurity A and with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in *water* and dilute to 20.0 ml with *water*.

Reference solution (a). A solution containing 0.0644 per cent w/v of *sodium bromide* and 0.0824 per cent w/v of *sodium chloride* in *water*. Dilute 1.0 ml of the solution to 50.0 ml with *water*.

Reference solution (b). A 0.00824 per cent w/v solution of *sodium chloride* in *water*. Dilute 1.0 ml of the solution to 25.0 ml with *water*.

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with strong anion exchange resin (13 µm),
- mobile phase: a solution containing 0.0063 per cent w/v of *sodium hydrogen carbonate* and 0.0212 per cent w/v of *anhydrous sodium carbonate* in *water,*
- flow rate: 2 ml per minute,
- conductivity detector set at 100 µs/v and maintained at 30°, use a self-regenerating anion suppressor at 100 mA,
- injection volume: 25 µl,

The retention time of chloride and bromide are about 1.7 minutes and about 2.8 minutes, respectively.

Inject reference solution (a). The test is not valid unless the resolution between the peaks due to chloride and bromide is not less than 2.5.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to chloride is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

2-Propanol. Not more than 1.0 per cent, determined by method described under Residual solvents (5.4).

Heavy metals (2.3.13). 1 g complies with limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Water (2.3.43). Not more than 4.5 per cent, determined on 0.4 g.

Assay. Dissolve 0.4 g in 40 ml of *glacial acetic acid*. Titrate with *0.1M perchloric acid*, determining the end- point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.06097 g of $C_{32}H_{53}BrN_2O_4$.

Storage. Store protected from light and moisture, and a temperature below - 15°.

2.4.26 Solubility.

Rocuronium Bromide. Freely soluble in *water* and *ethanol*, very soluble in *methylene chloride*.