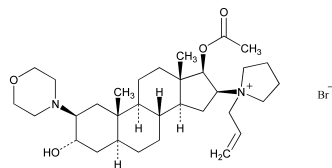


**Add the following:**

**Rocuronium Bromide**



C<sub>32</sub>H<sub>53</sub>BrN<sub>2</sub>O<sub>4</sub> 609.68

Pyrrolidinium, 1-[(2β,3α,5α,16β,17β)-17-(acetyloxy)-3-hydroxy-2-(4-morpholinyl)androstan-16-yl]-1-(2-propenyl)-, bromide.  
1-Allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium bromide, 17-acetate [119302-91-9].

**Change to read:**

» Rocuronium Bromide contains not less than 98.0 percent and not more than 102.0 percent of C<sub>32</sub>H<sub>53</sub>BrN<sub>2</sub>O<sub>4</sub>, calculated on the anhydrous and 2-propanol-free or acetic acid-free<sup>•</sup>(RB 1-Aug-2009) basis.

**Packaging and storage**—Preserve in tight containers, protected from light and moisture. Store at -20° or below.

**USP Reference standards** (11)—*USP Rocuronium Bromide RS*.  
*USP Rocuronium Peak Identification Mixture RS*.

**Identification**—

**A:** *Infrared Absorption* (197M).

**B:** The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

**C:** A solution (1 in 100) meets the requirements of the silver nitrate test for *Bromide* (191).

**Color of solution** (631)—

*Reference solution*—Mix 33 mL of *Matching Fluid G* and 67 mL of water.

*Test solution*—Transfer 500 mg of Rocuronium Bromide to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

*Procedure*—Proceed as directed for *Color and Achromicity* (631): the *Test solution* is not more intensely colored than the *Reference solution*.

**Specific rotation** (781S): between 28.5° and 32.0°, measured on an anhydrous and solvent-free basis at 20°.

*Test solution:* 10 mg per mL, in 0.05 M hydrochloric acid.

**Change to read:**

**pH** (791): between 7.0 and 9.5<sup>•</sup>(RB 1-Aug-2009) in a solution (1 in 100).

**Water, Method Ic** (921): not more than 4.0%.

**Residue on ignition** (281): not more than 0.1%.

**Heavy metals, Method II** (231): 0.001%.

**Add the following:**

**Limit of acetic acid**—[NOTE—Perform this test only if acetic acid is a known organic manufacturing process impurity.]

*Mobile phase*—Dissolve 6.1 g of sodium perchlorate in 800 mL of water. Adjust with 1 N sulfuric acid to a pH of 2.0. Dilute with water to 1 L, and mix. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

*Test solution*—Transfer about 60 mg of Rocuronium Bromide, accurately weighed, to a 10-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix (sonication may be needed for dissolution).

*Standard solution*—Dissolve an accurately weighed quantity of glacial acetic acid in *Mobile phase* to obtain a solution having a concentration of 0.2 mg of acetic acid per mL.

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the retention time of the acetate peak is about 3.8 minutes; the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 1.8; and the relative standard deviation for three replicate injections is not more than 5.0%.

*Procedure*—Separately inject equal volumes (about 20 μL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the acetate peaks. Calculate the percentage of acetic acid in the portion of Rocuronium Bromide taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C<sub>S</sub> is the concentration, in mg per mL, of glacial acetic acid in the *Standard solution*; C<sub>T</sub> is the concentration, in mg per mL, of Rocuronium Bromide in the *Test solution*; and r<sub>U</sub> and r<sub>S</sub> are the peak responses for acetic acid obtained from the *Test solution* and *Standard solution*, respectively: the content of acetic acid is not more than 5.0%<sup>•</sup>(RB 1-Aug-2009)

**Limit of 2-propanol**—

[NOTE—Perform this test only if 2-propanol is a known organic manufacturing process impurity.]

*Stock standard solution*—Transfer 35.0 μL of ethyl ether, 32.0 μL of 2-propanol, and 19.0 μL of methylene chloride to a 100-mL volumetric flask containing 90 mL of dimethylformamide (DMF), dilute with DMF to volume, and mix.

*Standard solution*—Transfer 2.5 mL of the *Stock standard solution* to a 25-mL volumetric flask containing 20 mL of DMF, dilute with DMF to volume, and mix.

*Working standard solution*—Transfer 1.0 mL of the *Standard solution* and 4.0 mL of water to a 20-mL headspace vial. Immediately close the vial with a cap, and mix.

*Test solution*—Transfer about 50 mg of Rocuronium Bromide, accurately weighed, to a 20-mL headspace vial. Dissolve in 1.0 mL of DMF. Add 4 mL of water, immediately close the vial with a cap, and mix.

## 2 Rocuronium

**Chromatographic system** (see *Chromatography* (621))—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 60-m fused silica column coated with a 1.8-μm layer of liquid phase G43. The carrier gas is helium or nitrogen with a linear velocity of about 55 cm or nitrogen with a linear velocity of about 25 cm per second and a split ratio of 1 : 6. The gas chromatograph is also equipped with a headspace autosampler, which is operated as follows: sample equilibration temperature is 90°; sample equilibration time is 15 minutes; transfer-line temperature is 140°; carrier gas is helium or nitrogen; and the pressurization time is 30 seconds. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 50° for 8 minutes, then the temperature is increased at a rate of 20° per minute to 250°, and maintained at 250° for 8 minutes. The injection port temperature is maintained at 140°, and the detector temperature is maintained at 280°. Chromatograph the *Working standard solution*, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.87, 1.0, and 1.08 for ethyl ether, 2-propanol, and methylene chloride, respectively; the resolution, *R*, between ethyl ether and 2-propanol is not less than 1.0; the resolution, *R*, between 2-propanol and methylene chloride is not less than 1.0; and the relative standard deviation for replicate injections is not more than 10.0% for the 2-propanol peak.

**Procedure**—Separately inject equal volumes of the headspace (about 1 mL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of 2-propanol in the portion of Rocuronium Bromide taken by the formula:

$$100(r_U / r_S) (V \times 0.786 / W) / 1000$$

in which  $r_U$  and  $r_S$  are the 2-propanol peak responses obtained from the *Test solution* and the *Working standard solution* chromatograms, respectively;  $V$  is the volume, in μL, of 2-propanol taken to prepare the *Stock standard solution*; 0.786 is the relative density of 2-propanol, in mg per μL;  $W$  is the weight, in mg, of Rocuronium Bromide taken to prepare the *Test solution*; and 1000 is the dilution factor for the *Standard solution*. Not more than 1.0% of 2-propanol is found.

**Related compounds—**

**Mobile phase**—Proceed as directed in the *Assay*.

**Diluent**—Prepare a mixture of acetonitrile and water (9 : 1).

**Peak identification solution**—Dissolve a suitable quantity of USP Rocuronium Peak Identification Mixture RS in a suitable volume of *Diluent* to obtain a solution having a concentration of about 1 mg per mL.

**Standard solution**—Quantitatively dilute the *Standard preparation* from the *Assay* with *Diluent* to obtain a solution having a known concentration of about 0.01 mg per mL.

**Test solution**—Transfer about 100 mg of Rocuronium Bromide, accurately weighed, to a 10-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

**Chromatographic system**—Prepare as directed in the *Assay*. Chromatograph the *Peak identification solution*, and record the peak areas as directed for *Procedure*, identifying the peaks by using the relative retention times given in *Table 1*: the ratio of the height of the rocuronium related compound H peak to the height of the valley between the rocuronium related compound H peak and the rocuronium peak is not less than 1.5; and the resolution, *R*, between rocuronium and rocuronium related compound C is not less than 3.5.

**Procedure**—Separately inject equal volumes (about 5 μL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the chromatogram to run 2.5 times longer than the retention time for rocuronium. Measure all of the peak areas in the *Test solu-*

*tion*. Calculate the percentage of each impurity in the portion of Rocuronium Bromide taken by the formula:

$$100 (C_S / C_T)(r_U / r_S)(1 / F)$$

in which  $C_S$  is the concentration, in mg per mL, of USP Rocuronium Bromide RS in the *Standard solution*;  $C_T$  is the concentration, in mg per mL, of Rocuronium Bromide in the *Test solution*;  $r_U$  is the peak area for any impurity in the *Test solution*;  $r_S$  is the peak area for rocuronium bromide obtained from the *Standard solution*; and  $F$  is the relative response factor, obtained from *Table 1*, for each of the known impurities relative to rocuronium bromide.

**Table 1**

Compound Name	Relative Retention Time	Relative Response Factor ( <i>F</i> )	Limit (%)
Rocuronium related compound A <sup>1</sup>	About 0.20	2.1	0.2
Rocuronium related compound G <sup>2</sup>	About 0.44	2.3	0.1
Rocuronium related compound F <sup>3</sup>	About 0.75	0.79	0.1
Rocuronium related compound B <sup>4</sup>	About 0.80	1.0	0.3
Rocuronium related compound D <sup>5</sup>	About 0.90	1.0	0.1
Rocuronium related compound H <sup>6</sup>	About 0.95	2.9	0.1
Rocuronium bromide	1.0	—	—
Rocuronium related compound C <sup>7</sup>	About 1.20	1.0	0.3
Rocuronium related compound E <sup>8</sup>	About 1.53	1.0	0.1
Any individual unspecified impurity	—	—	0.10
<b>Total impurities</b>	—	—	<b>1.5</b>

<sup>1</sup>3α-Hydroxy-2β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstan-17β-yl acetate.  
<sup>2</sup>2β-(Morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstan-3α,17β-diol.  
<sup>3</sup>1-[3α,17β-Bis(acetyloxy)-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.  
<sup>4</sup>1-[3α,17β-Bis(acetyloxy)-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.  
<sup>5</sup>1-[3α-(Acetyloxy)-17β-hydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.  
<sup>6</sup>1-[17β-(Acetyloxy)-2-(morpholin-4-yl)-3-oxo-5α-androst-1-en-16β-yl]-1-(prop-2-enyl)pyrrolidinium.  
<sup>7</sup>1-[3α,17β-Dihydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.  
<sup>8</sup>1-[17β-(Acetyloxy)-3α-hydroxy-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

Disregard any peak eluting before rocuronium bromide related compound A, and any peak with an area less than 0.5 times that of the principal peak in the chromatogram obtained from the *Standard solution*.

**Assay—**  
**Diluent:** a mixture of acetonitrile and water (9 : 1).  
**Buffer solution**—Transfer 4.53 g of tetramethylammonium hydroxide pentahydrate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust the solution with phosphoric acid to a pH of 7.4, and mix.

**Mobile phase**—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (9 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

*Standard preparation*—Dissolve an accurately weighed quantity of USP Rocuronium Bromide RS in *Diluent*, and dilute quantitatively with *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

*Assay preparation*—Transfer an accurately weighed quantity of Rocuronium Bromide to a suitable volumetric flask to obtain a solution having a nominal concentration of about 1 mg per mL of rocuronium bromide. Dissolve in and dilute with *Diluent* to volume, and mix.

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-μm packing L3. The flow rate is about 2.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the tailing factor is not more than 2.0; and the relative standard deviation for replicate in-

jections is not more than 2.0% for the rocuronium bromide peak. [NOTE—The system may need equilibration for 4 hours.]

*Procedure*—Separately inject equal volumes (about 5 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in percentage, of C<sub>32</sub>H<sub>53</sub>BrN<sub>2</sub>O<sub>4</sub> in the portion of Rocuronium Bromide taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which  $C_S$  is the concentration, in mg per mL, of USP Rocuronium Bromide RS in the *Standard preparation*;  $C_U$  is the nominal concentration, in mg per mL, of Rocuronium Bromide in the *Assay preparation*; and  $r_U$  and  $r_S$  are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■<sup>1S</sup> (USP32)