

BRIEFING

Rocuronium Bromide. This monograph proposal was published on the USP Website as a draft USP Pending Standard for public comments. The MD-PP Expert Committee has reviewed all the comments that were received and has approved the monograph as an Authorized USP Pending Standard. The following is a summary of the comments received and the Expert Committee's responses.

Comment 1: Commenter recommended replacing the word "pyrrolidin" in the first of the three chemical names with "morpholin".

Response: Comment incorporated.

Comment 2: Four commenters indicated that acetic acid is not used in their manufacturing process and therefore requested that the test for *Limit of acetic acid* be removed from the proposal.

Response: Comment incorporated by making the test mandatory only if acetic acid is likely to be present in the drug substance. Because the proposed test is a limit test, the Expert Committee has revised the text to "not more than 4.5%" instead of the range previously indicated.

Comment 3: Three commenters indicated that their drug substance would fail the pH requirement and requested the range to be widened to match the upper limit of *European Pharmacopeia 5.08*.

Response: Comment incorporated by raising the upper limit.

Comment 4: Commenter requested the revision of the relative response factors in the test for *Related compounds* to be consistent with *European Pharmacopeia 5.08*. **Response:** Comment incorporated.

Comment 5: Commenter requested the revision of the limits of specified impurities in the test for *Related compounds* to be consistent with those in *European Pharmacopeia 5.08*.

Response: Comment incorporated.

Comment 6: Commenter requested that a test for *Bromide content* be included.

Response: Comment not incorporated because it does not add value to the public standard. Examples of recent monographs where counter ion content was not included are *Citalopram Hydrobromide*, *Tizanidine Hydrochloride*, and *Tiagabine Hydrochloride*.

Comment 7: Commenter requested that the parameters in the test for *Color of solution* match the parameters specified in *European Pharmacopeia 5.08*.

Response: Comment incorporated.

Comment 8: Commenter requested that the storage temperature be revised from "2° to 8°" to "–20°".

Response: Comment not incorporated because *European Pharmacopeia 5.08* does not require storage at –20°.

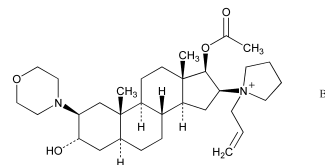
The HPLC procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Hypersil silica brand of L3 column. The typical retention time for rocuronium is about 8 minutes. The test for *Limit of acetic acid* is based on analyses performed with the BDS Hypersil C18 brand of L1 column. The typical retention time for acetic acid is about 3.8 minutes.

(MD-PP: R. Ravichandran) RTS—C49321

Add the following:

■ **Rocuronium Bromide**

v. 1 Authorized November 1, 2007



C₃₂H₅₃BrN₂O₄ 609.68

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

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].

» Rocuronium Bromide contains not less than 98.0 percent and not more than 102.0 percent of C₃₂H₅₃BrN₂O₄, calculated on the anhydrous and solvent-free basis. If acetic acid is present, the content is calculated on the anhydrous and acetic acid-free basis.

Packaging and storage—Preserve in tight containers, protected from light and moisture. Store between 2° and 8°.

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Labeling—If acetic acid is present, indicate that on the label appropriately.

USP Reference standards <11>— *USP Rocuronium Bromide 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 10) 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 under *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° at 25°.

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

pH <791>: between 7.0 and 9.5, in a solution (1 in 100).

Water, Method I <921>: not more than 4.0%.

Residue on ignition <281>: not more than 0.1%.

Heavy metals, Method II <231>: 0.001%.

Limit of acetic acid—[NOTE—Perform this test only if acetic acid is used in the manufacturing process]

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_s is the concentration, in mg per mL, of glacial acetic acid in the *Standard solution*; C_T is the concentration, in mg per mL, of rocuronium bromide in the *Test solution*; and r_U and r_S 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 4.5%.

Related compounds—

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

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

Resolution solution—Transfer about 30 mg of USP Rocuronium Bromide RS to a 20.0-mL volumetric flask. Add 2 drops of dilute ammonium hydroxide (1 in 5) and 5 mL of water, and mix to dissolve. Heat the solution over a water bath at 85° for 30 minutes. Cool the solution, and dilute with acetonitrile to volume.

Acetate identification solution—Transfer about 150 mg of glacial acetic acid to a 100.0-mL volumetric flask. Dilute with *Diluent* to volume, and mix.

Standard solution—Dissolve an accurately weighed quantity of USP Rocuronium Bromide RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, 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 10.0-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system—Prepare as directed in the *Assay*. Chromatograph the *Resolution solution* and the *Acetate 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 resolution, *R*, between rocuronium and rocuronium bromide 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 solution*. Calculate the percentage of each impurity in the portion of Rocuronium Bromide taken by the formula:

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

Compound name	Relative Retention Time	Relative Response Factor	Limit (%)
Rocuronium Bromide Related Compound A ¹	About 0.20	2.1	0.2
Acetate ²	About 0.26	—	—
Rocuronium Bromide Related Compound G ³	About 0.44	2.3	0.1
Rocuronium Bromide Related Compound F ⁴	About 0.76	0.79	0.1
Rocuronium Bromide Related Compound B ⁵	About 0.80	1.0	0.3
Rocuronium Bromide Related Compound D ⁶	About 0.90	1.0	0.1
Rocuronium Bromide Related Compound H ⁷	About 0.95	2.9	0.1
Rocuronium Bromide	1.0	—	—
Rocuronium Bromide Related Compound C ⁸	About 1.20	1.0	0.3
Rocuronium Bromide Related Compound E ⁹	About 1.53	1.0	0.1
Any individual unspecified impurity	—	—	0.10
Total impurities	—	—	1.5

¹ 3α-Hydroxy-2β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstan-17β-yl acetate.

² Quantified in the test for *Limit of acetic acid*.

³ 2β-(Morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstan-3α,17β-diol.

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

⁵ 1-[3α,17β-Bis(acetyloxy)-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium bromide.

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

⁷ 1-[17β-(Acetyloxy)-2-(morpholin-4-yl)-3-oxo-5α-androst-1-en-16β-yl]-1-(prop-2-enyl)pyrrolidinium bromide.

⁸ 1-[3α,17β-Dihydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium bromide.

⁹ 1-[17β-(Acetyloxy)-3α-hydroxy-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium bromide.

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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.

Disregard the peak due to the bromide ion eluting just before rocuronium bromide related compound A, the peak due to acetic acid, 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—

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* (90 : 10). 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 10 mg per mL.

Assay preparation—Transfer about 100 mg of Rocuronium Bromide, accurately weighed, to a 10.0-mL volumetric flask. 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 injections 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 $C_{32}H_{53}BrN_2O_4$ 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 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. ■