Standard preparation—Dissolve an accurately weighed quantity of USP Sodium Lactate RS in water to obtain a solution having a known concentration of about 0.6 mg per mL.

Assay preparation—Use undiluted Injection.

Procedure—Proceed as directed in the *Assay for lactate* under *Lactated Ringer's Injection*. Calculate the concentration, in mg per mL, of lactate ($C_3H_5O_3$) in the *Assay preparation* taken by the formula:

$$C(89.07 / 112.06)(r_U / r_S)$$

in which the terms are as defined therein.

Assay for dextrose—Proceed with Injection as directed in the *Assay for dextrose* under *Ringer's and Dextrose Injection*.

Ringer's Irrigation

» Ringer's Irrigation is Ringer's Injection that has been suitably packaged, and it contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose glass or plastic containers. Glass containers are preferably of Type I or Type II glass. The container may be designed to empty rapidly and may contain a volume of more than 1 L.

Labeling—The designation "not for injection" appears prominently on the label.

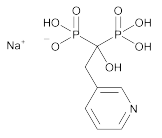
USP Reference standards ⟨11⟩—
USP Endotoxin RS

Bacterial endotoxins ⟨85⟩—It contains not more than 0.5 USP Endotoxin Unit per mL.

Sterility ⟨71⟩: meets the requirements.

Other requirements—It responds to the *Identification* tests, and meets the requirements for *pH*, *Heavy metals*, *Assay for calcium*, *Assay for potassium*, *Assay for sodium*, and *Assay for chloride* under *Ringer's Injection*.

Risedronate Sodium



$C_7H_{10}NNaO_7P_2$ 305.09

$C_7H_{10}NNaO_7P_2 \cdot H_2O$ 323.12

$C_7H_{10}NNaO_7P_2 \cdot 2.5\ H_2O$ 350.13

Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt;
Sodium trihydrogen [1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate;
Hemi-pentahydrate [329003-65-8].
Monohydrate [353228-19-0].

DEFINITION

Risedronate Sodium contains one or two and one-half molecules of hydration. The monohydrate form contains NLT 98.0% and NMT 102.0% of $C_7H_{10}NNaO_7P_2$, calculated on the dried basis. The hemi-pentahydrate form contains NLT 98.0% and NMT 102.0% of $C_7H_{10}NNaO_7P_2$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨197⟩**:** The spectra of trifluorovinyl chloride polymer and mineral oil dispersions of it, separately prepared from a test specimen, exhibit maxima in the regions of 4000 to 1350 cm^{-1} and 1350 to 450 cm^{-1}, respectively, only at the same wavelengths as those of similar preparations of USP Risedronate Sodium RS. [NOTE—If a difference appears in the infrared spectra of the analyte and the standard, dissolve equal portions of the test specimen and the USP Reference Standard in equal volumes of water containing about 50 mg/mL of potassium bromide. Evaporate the solutions to dryness at 105° for 120 min. Repeat the test on the residues.]
- **B. Identification Tests—General,** *Sodium* ⟨191⟩**:** It meets the requirements of the flame test.

ASSAY

- **Procedure**

Mobile phase: 1.8 g/L of edetate disodium in water. Adjust with 1 N sodium hydroxide to a pH of 9.5 ± 0.1.

Standard solution: Dissolve USP Risedronate Sodium RS and USP Risedronate Related Compound A RS in *Mobile phase* to obtain a solution containing 1.0 mg/mL of anhydrous risedronate sodium and 0.1 mg/mL of risedronate related compound A.

Sample solution: 1.1 mg/mL of Risedronate Sodium in *Mobile phase*

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 263 nm
Column: 4.0-mm × 25-cm; 10-µm packing L48
Flow rate: 0.8 mL/min
Injection size: 20 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 2.3 between risedronate and risedronate related compound A
Tailing factor: NMT 1.6 for the risedronate peak
Relative standard deviation: NMT 1.0% for the risedronate peak from three replicate injections

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of risedronate sodium ($C_7H_{10}NNaO_7P_2$) in the portion of Risedronate Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Risedronate Sodium RS in the *Standard solution* (mg/mL)
C_U = concentration of Risedronate Sodium in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis for the monohydrate form or on the anhydrous basis for the hemi-pentahydrate form

IMPURITIES

- **Heavy Metals**

Lead nitrate solution: Add 1 mL of nitric acid to 100 mL of water. Dissolve 100 mg of lead nitrate in it, and dilute with water to 1000 mL.

Sodium bicarbonate solution: Transfer 0.840 g of sodium bicarbonate to a 1000-mL volumetric flask containing about 950 mL of water. Dissolve in and dilute with water to volume. Adjust with 0.1 N sodium hydroxide or 0.1 N hydrochloric acid, as necessary, to a pH of 4.40 ± 0.02.

Hydrogen sulfide solution: Transfer 200 mL of *Sodium bicarbonate solution* to a suitable conical flask, and bubble hydrogen sulfide gas through the solution until it turns a strip of lead acetate test paper black (see *Reagents, Indicators, and Solution—Indicator and Test Papers*).

Standard solutions: Transfer 500 mg of Risedronate Sodium to each of three separate beakers. Add 41 mL of water to each beaker, and stir to dissolve. Adjust with 0.1 N sodium hydroxide or 0.1 N hydrochloric acid, as necessary, to a pH of 4.40 ± 0.02. Label the first beaker as *Standard solution 1*. Add 200 µL of *Lead nitrate solution* to the second beaker (*Standard solution 2*) and 400 µL to the third beaker (*Standard solution 3*). These solutions contain the equivalent of 0, 12.5, and 25 µg of lead (representing 0, 10, and 20 ppm, respectively).

Sample solution: Transfer 1.75 g of Risedronate Sodium to a suitable beaker. Add 41 mL of water, and stir to dissolve. Adjust with 0.1 N sodium hydroxide or 0.1 N hydrochloric acid, as necessary, to a pH of 4.40 ± 0.02.

Analysis: Add 7 mL of *Hydrogen sulfide solution* to each of the beakers containing the *Standard solutions* and the *Sample solution.* Allow the solutions to stand for at least 5 min. Add 60 µL of 1 N hydrochloric acid to each of the beakers containing the *Standard solutions,* add 200 µL of 1 N hydrochloric acid to the beaker containing the *Sample solution*, and stir. Transfer the solutions into 50-mL color-comparison tubes, and view downward over a white surface.

Acceptance criteria: The color of the solution obtained from the *Sample solution* is not darker than that of the solution from *Standard solution 3* (NMT 20 ppm).

• **ORGANIC IMPURITIES, PROCEDURE 1**

[NOTE—Perform both *Procedure 1* and *Procedure 2*.]

Mobile phase, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Diluted standard solution: Dilute a portion of the *Standard solution* with *Mobile phase* to obtain a solution containing 5 µg/mL of anhydrous risedronate sodium and about 0.5 µg/mL of risedronate related compound A.

System suitability

Samples: *Standard solution* and *Diluted standard solution*

Suitability requirements

Resolution: NLT 2.3 between risedronate related compound A and risedronate, *Standard solution*

Tailing factor: NMT 1.6 for the risedronate peak, *Standard solution*

Relative standard deviation: NMT 1.0% for the risedronate peak from three replicate injections, *Standard solution*; NMT 15% for the risedronate related compound A peak from three replicate injections, *Diluted standard solution*

Analysis

Samples: *Sample solution* and *Diluted standard solution*

Calculate the percentage of each impurity in the portion of Risedronate Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of risedronate from the *Diluted standard solution*

C_S = concentration of USP Risedronate Sodium RS in the *Diluted standard solution* (mg/mL)

C_U = concentration of Risedronate Sodium in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 1*)

Table 1

Name	Relative Response Factor	Relative Retention Time
3-Pyridyl acetic acid	1.65	0.22
2-Pyridinyl isomer (USP Risedronate Related Compound A RS)	1.0	0.84
Risedronate sodium	—	1.0

Acceptance criteria

Any individual impurity: NMT 0.10%

[NOTE—Disregard the peak due to the sodium ion, eluting at about 1.6 min, and any peak observed in the blank. The reporting level for impurities is 0.05%.]

• **ORGANIC IMPURITIES, PROCEDURE 2**

Mobile phase: Transfer 16.15 g of dibasic potassium phosphate and 0.46 g of edetate disodium to a 1-L beaker, and dissolve in about 400 mL of water. Add 1 vial of commercially available tetrabutylammonium dihydrogen phosphate buffered solution in methanol[1] and 1 mL of hydrochloric acid. Adjust with 1 N sodium hydroxide or 1 N hydrochloric acid, as necessary, to a pH of 7.5 ± 0.1, and dilute with water to 480 mL. Add 20 mL of methanol, mix well, pass the solution through a nylon filter of 0.45-µm pore size, and degas.

Diluent: Transfer 0.46 g of edetate disodium to a 1-L beaker, and dissolve in 500 mL of water. Adjust with 1 N sodium hydroxide to a pH of 7.5 ± 0.1.

Standard solution: 5 µg/mL of USP Risedronate Related Compound B RS in *Diluent*

Diluted standard solution: 0.5 µg/mL of USP Risedronate Related Compound B RS in *Diluent* from the *Standard solution*

Sample solution: 2 mg/mL of Risedronate Sodium, in *Diluent*, using sonication if necessary

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 263 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.0 mL/min

Injection size: 10 µL

System suitability

Samples: *Standard solution* and *Diluted standard solution*

Suitability requirements

Capacity factor: Greater than 2, *Standard solution*

Tailing factor: Less than 1.5, *Standard solution*

Relative standard deviation: NMT 5% from three replicate injections, *Standard solution*

Relative standard deviation: NMT 10% from three replicate injections, *Diluted standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—Disregard any peak eluting before risedronate related compound B. The risedronate peak elutes unretained at the void volume.]

Calculate the percentage of each impurity in the portion of Risedronate Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of risedronate related compound B from the *Standard solution*

C_S = concentration of USP Risedronate Related Compound B RS in the *Standard solution* (mg/mL)

C_U = concentration of Risedronate Sodium in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of risedronate related compound B as a free acid, 530.20

M_{r2} = molecular weight of risedronate related compound B as a tetrahydrate disodium salt, 646.22

Acceptance criteria

Risedronate related compound B: NMT 0.10%

Individual impurities: NMT 0.10%

Total impurities: NMT 0.50%, *Procedure 1* and *Procedure 2* being combined

[NOTE—Disregard any peak observed in the blank. The reporting level for impurities is 0.05%.]

[1] Available from Waters Corp. as Part #85101 (PIC A).

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method Ic* ⟨**921**⟩ (where it is labeled as a hemi-pentahydrate)**:** 11.9%–13.9%. Perform the test by direct introduction of solid sample into the titrator. Alternatively, *Method 1a* may be used.
- **LOSS ON DRYING** ⟨**731**⟩ (where it is labeled as a monohydrate) (See *Thermal Analysis* ⟨891⟩.)
  Determine the percentage of volatile substances by thermogravimetric analysis on an appropriately calibrated instrument, using 7–15 mg of Risedronate Sodium. Heat the specimen under test at a rate of 10°/min in a stream of nitrogen at a flow rate of about 40 mL/min. Record the thermogram from ambient temperature to 250°.
  Acceptance criteria: It loses between 5.5% and 7.5% of its weight.

ADDITIONAL REQUIREMENTS

- **LABELING:** Label to indicate whether it is the monohydrate or the hemi-pentahydrate form.
- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Risedronate Related Compound A RS
  2-Pyridinyl isomer [1-hydroxy-2-(2-pyridinyl)ethylidene] bis(phosphonic acid) monohydrate.
  $C_7H_{11}NO_7P_2$ 283.12
  USP Risedronate Related Compound B RS
  Cyclic dimer, disodium tetrahydrate salt, [3,6-bis[(3-pyridinyl)methyl]-2,5-dihydroxy-2,5-dioxido-1,4,2,5-dioxadiphosphorinane-3,6-diyl]bis[phosphonic acid] disodium tetrahydrate salt.
  $C_{14}H_{16}N_2O_{12}P_4Na_2 \cdot 4H_2O$ 646.22
  USP Risedronate Sodium RS

Risedronate Sodium Tablets

» Risedronate Sodium Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of risedronate sodium ($C_7H_{10}NNaO_7P_2$).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—**
USP Risedronate Sodium RS
USP Risedronate Related Compound A RS
2-Pyridinil isomer [1-hydroxy-2-(2-pyridinyl)ethylidene] bis(phosphonic acid) monohydrate.
$C_7H_{11}NO_7P_2$ 283.12
USP Risedronate Related Compound C RS
[2-(3-Pyridinyl)ethylidene-1,1]bis(phosphonic acid).
$C_7H_{11}NO_6P_2$ 267.11

Identification—

A: *Infrared Absorption* ⟨197K⟩

Test specimen—Transfer a quantity of Tablets, equivalent to about 50–75 mg of risedronate sodium, to a suitable flask, add 10 mL of water, and shake. Pass first through a suitable paper filter and then through a 0.45-µm nylon filter. Add 10 mL of 0.2 M cupric chloride solution, mix well, and allow the solution to stand for about 10 minutes. Add 2 mL of dehydrated alcohol, mix well, and allow the solution to stand for a minimum of one hour, to form a blue precipitate of the copper complex. Collect the precipitate using a 0.45-µm nylon filter, wash it with 10 mL of dehydrated alcohol, and allow it to dry on the filter. [NOTE—Dry the precipitate under ambient conditions; do not heat the precipitate. A modest change of color (from blue to green) may be observed upon drying.]

Standard specimen—Dissolve about 50 mg of USP Risedronate Sodium RS in 10 mL of water, and pass the solution through a 0.45-µm nylon filter. Proceed as directed under *Test specimen,* beginning with "Add 10 mL of 0.2 M cupric chloride solution..."

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.*

Dissolution ⟨711⟩**—**

FOR TABLETS LABELED TO CONTAIN 5 MG OR 30 MG OR 35 MG:

Medium: water; 500 mL, deaerated.

Apparatus 2: 50 rpm, paddles coated with Teflon.

Time: 30 minutes.

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

Standard solution—Transfer an accurately weighed quantity of USP Risedronate Sodium RS to a suitable volumetric flask, and dilute with *Medium* to volume to obtain a solution having a known concentration of about 1 mg of anhydrous risedronate sodium per mL. Further dilute this solution with *Medium* to obtain a final concentration of about (0.002 × L) mg per mL, where L is the tablet label claim in mg.

Test solution—Use a portion of the solution under test, filtering if necessary.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 263-nm detector and a 4.0-mm ×5-cm column that contains 10-µm packing L48. The flow rate is about 0.8 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for multiple injections is not more than 2%.

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 peak responses. Calculate the percentage of risedronate sodium dissolved by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times L}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *L* is the tablet label claim in mg.

Tolerances—Not less than 80% (*Q*) of the labeled amount of risedronate sodium is dissolved in 30 minutes.

FOR TABLETS LABELED TO CONTAIN AT LEAST 75 MG:

Medium: water; 900 mL, deaerated.

Apparatus 2: 50 rpm, paddles coated with Teflon.

Time: 45 minutes.

Standard solution—Transfer an accurately weighed quantity of USP Risedronate Sodium RS to a suitable volumetric flask and dilute with *Medium* to volume to obtain a solution having a known concentration of about 0.12 mg of anhydrous risedronate sodium per mL.

Test solution—Use a portion of the solution under test. Dilute further with *Medium,* if necessary.

Procedure—Determine the amount of risedronate sodium dissolved by employing UV absorption at the wavelength of maximum absorbance at about 263 nm, with a background correction at 400 nm on portions of the *Test solution,* in comparison with a *Standard solution,* using the *Medium* as a blank and a 5-mm path-length cell. Calculate the percentage of risedronate sodium dissolved by the formula:

$$\frac{A_U \times C_S \times D \times 900 \times 100}{A_S \times L}$$