9-Hydroxyrisperidone-(6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

6-Methylrisperidone-(6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

[NOTE—This mixture contains risperidone, *Z*-oxime, 9-hydroxyrisperidone, and 6-methylrisperidone.]

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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*.

Loss on drying ⟨731⟩**—**Dry in vacuum at 80° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%, a 2.0-g test specimen being used.

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

Related compounds—

Buffer solution, Solution A, Solution B, Mobile phase, Diluent, System suitability solution, and *Chromatographic system*—Prepare as directed in the *Assay*.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay*.

Test solution—Use the *Assay preparation*.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the chromatogram. Identify the impurities using the relative retention times given in *Table 1,* and measure the peak responses. Calculate the percentage of each risperidone related compound in the portion of Risperidone taken by the formula:

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

in which C_S and C_U are the concentrations, in mg per mL, of risperidone in the *Standard solution* and the *Test solution* respectively; r_U is the peak area of each impurity obtained from the *Test solution;* r_S is the peak area of risperidone obtained from the *Standard solution;* and F is the relative response factor for each impurity relative to risperidone. In addition to not exceeding the limits in *Table 1,* not more than 0.10% of any unknown impurity (use F value of 1.0) is found and not more than 0.30% of the total impurities is found. Disregard the impurity peaks that are less than 0.05%.

Table 1

Related Compound	Relative Retention Time (RRT)	Relative Response Factor (*F*)	Limit (%)
E-oxime[1]	0.60	1.0	NMT 0.20
Z-oxime[2]	0.67	0.63	NMT 0.20
9-hydroxyrisperidone[3]	0.76	0.92	NMT 0.20
5-fluororisperidone[4]	0.94	1.0	NMT 0.20
Risperidone	1.0	1.0	—
6-methylrisperidone[5]	1.2	0.95	NMT 0.20

[1]3-[2-[4-[(*E*)-(2,4-Difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

[2]3-[2-[4-[(*Z*)-(2,4-Difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

[3](9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

[4]3-[2-[4-(5-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

[5](6*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

Assay—

Buffer solution—Dissolve 15.4 g of ammonium acetate in 1 L of water. Adjust with 10% acetic acid to a pH of 6.5, and mix.

Solution A—Mix 100 mL of *Buffer solution* with 150 mL of methanol in a 1000-mL volumetric flask, and dilute with water to volume.

Solution B—Mix 100 mL of *Buffer solution* with 850 mL of methanol in a 1000-mL volumetric flask, and dilute with water to volume.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Mix 100 mL of *Buffer solution* with 900 mL of water and 1000 mL of methanol.

System suitability solution—Prepare a 1 mg per mL solution of USP Risperidone System Suitability Mixture RS in *Diluent*.

Standard preparation—Dissolve an accurately weighed quantity of USP Risperidone RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Risperidone in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a concentration of about 1.0 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 275-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–1	70	30	isocratic
1–20	70→5	30→95	linear gradient
20–25	5	95	isocratic
25–27	5→70	95→30	linear gradient
27–35	70	30	re-equilbration

Inject the *System suitability solution*. Record the peak responses as directed for *Procedure,* and identify the peaks due to *Z*-oxime, 9-hydroxyrisperidone, 6-methylrisperidone, and risperidone using the relative retention times (RRT) from *Table 1*; the resolution, *R,* between *Z*-oxime and 9-hydroxyrisperidone is not less than 2.8; the tailing factor for risperidone is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% for the risperidone peak.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and measure the responses for the risperidone peak. Calculate the quantity, in percent of $C_{23}H_{27}FN_4O_2$, in the portion of Risperidone taken by the formula:

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

in which C_S and C_U are the concentrations, in mg per mL, of risperidone in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Risperidone Oral Solution

DEFINITION

Risperidone Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of risperidone ($C_{23}H_{27}FN_4O_2$). It may contain a suitable preservative.

IDENTIFICATION

- The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Buffer: 5.0 g/L of ammonium acetate in water
Mobile phase: Acetonitrile and *Buffer* (11:39)
Standard stock solution: 1 mg/mL of USP Risperidone RS, in methanol
Standard solution: 0.2 mg/mL of USP Risperidone RS prepared from the *Standard stock solution* as follows: Transfer 5.0 mL of the *Standard stock solution* to a 25-mL volumetric flask. Add 5.0 mL of water followed by 12.5 mL of *Buffer*, and allow to cool to room temperature. Dilute with methanol to volume.
Sample solution: Nominal concentration of 0.2 mg/mL of risperidone prepared from Oral Solution as follows: Transfer an amount of Oral Solution, equivalent to 5 mg of risperidone to a 25-mL volumetric flask, add 12.5 mL of *Buffer*, fill with methanol almost to volume, and mix well. Allow to cool to room temperature, and dilute with methanol to volume.
System suitability solution: 0.25 mg/mL of USP Risperidone Related Compounds Mixture RS prepared as follows: Weigh USP Risperidone Related Compounds Mixture RS into a suitable volumetric flask. Dissolve first in 20% of the flask volume of methanol. Add 20% of the flask volume of water followed by 50% of the flask volume of *Buffer*, and allow to cool to room temperature. Dilute with methanol to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 275 nm
Column: 4.6-mm × 10-cm; 3-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 10 µL
Run time: 2 times the retention time of risperidone
System suitability
Samples: *Standard solution* and *System suitability solution*
Relative retention times: See *Impurity Table 1*.
Suitability requirements
Resolution: NLT 1.5 between bicyclorisperidone and *Z*-oxime, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{23}H_{27}FN_4O_2$ in the portion of risperidone taken:

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

r_U = peak response for risperidone from the *Sample solution*
r_S = peak response for risperidone from the *Standard solution*
C_S = concentration of USP Risperidone RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of risperidone in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DELIVERABLE VOLUME** ⟨698⟩**:** Meets the requirements

IMPURITIES

Organic Impurities

- **PROCEDURE**

Buffer, Mobile phase, Sample solution, Chromatographic system, and **System suitability solution:** Proceed as directed in the *Assay*
Standard stock solution: 5 µg/mL of USP Risperidone RS, in methanol
Standard solution: 1 µg/mL of USP Risperidone RS from the *Standard stock solution* prepared as follows: Transfer 5.0 mL of the *Standard stock solution* to a 25-mL volumetric flask. Add 5.0 mL of water followed by 12.5 mL of *Buffer*, and allow to cool to room temperature. Dilute with methanol to volume.
System suitability
Samples: *System suitability solution* and *Standard solution*
Relative retention times: See *Impurity Table 1*.
Suitability requirements
Resolution: NLT 1.5 between bicyclorisperidone and *Z*-oxime, *System suitability solution*
Relative standard deviation: NMT 10%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of risperidone taken:

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

r_U = peak response for each individual impurity from the *Sample solution*
r_S = peak response for risperidone from the *Standard solution*
C_S = concentration of USP Risperidone RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of risperidone in the *Sample solution* (mg/mL)
F = relative response factor (see *Impurity Table 1*)
Acceptance criteria
Individual impurities: See *Impurity Table 1*.
Total impurities: NMT 1.0%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Risperidone *cis N*-oxide[a]	0.33	0.97	0.50
Bicyclorisperidone[b]	0.43	0.67	0.50
Z-Oxime[c]	0.53	—	—
Risperidone	1.0	—	—
Any unspecified degradation product	—	1.0	0.20

[a] *cis*-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one,*N*-oxide monohydrate.
[b] 3-(4-Fluoro-2-hydroxyphenyl)-1-[2-(6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido-[1,2-a]pyrimidin-3-yl)ethyl]-1-aza-2-azoniabicyclo[2.2.2]oct-2-ene salt.
[c] (*Z*)-3-[2-[4-(2,4-Difluorophenyl)(hydroxyimino)methyl]-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one.
[NOTE—Process impurity, not to be quantified in drug product: it is used to establish system suitability only.]

SPECIFIC TESTS

- **PH** ⟨791⟩**:** 2.0–4.0

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in light-resistant containers. Store at controlled room temperature. Do not freeze.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Risperidone RS
3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one
410.48 CAS-106266-06-2
USP Risperidone Related Compounds Mixture RS
Contains a 98.9:0.5:0.30:0.3 (area %) mixture of four compounds:
98.9% of*Risperidone*.

0.5% of *Risperidone cis-N-oxide: cis*-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one].
0.3% of *Bicyclorisperidone:* 3-(4-fluoro-2-hydroxyphenyl)-1-[2-(6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido-[1,2-*a*] pyrimidin-3-yl)ethyl]-1-aza-2-azoniabicyclo[2.2.2]oct-2-ene iodide.
0.3% of *Z-oxime:* (*Z*)-3-[2-[4-(2,4-difluorophenyl) (hydroxyimino)methyl]-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

Risperidone Tablets

» Risperidone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of risperidone ($C_{23}H_{27}FN_4O_2$).

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—**
USP Risperidone RS
3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one 410.48 CAS-106266-06-2

Identification—

A: *Infrared Absorption*—

Test solution—Grind an appropriate number of Tablets to prepare a 550 ± 50 µg per mL solution of risperidone in ethyl acetate. Shake the solution for 30 minutes, and centrifuge for 20 minutes. Evaporate 5 mL of the supernatant with the aid of a stream of nitrogen to 2 mL on a warm water bath. Add 150 ± 50 mg of KBr powder, mix well, and evaporate to dryness. Grind the dried mixture, and press a small amount into a transparent pellet ⟨197K⟩.

Standard solution—Grind about 2 mg of USP Risperidone RS with about 200 mg of KBr powder, and press into a transparent pellet.

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⟩**—**

Medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the amount of $C_{23}H_{27}FN_4O_2$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (65:35), and add 1 mL of trifluoroacetic acid to each 1 L of the mixture. Adjust with ammonium hydroxide to a pH of 3.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Risperidone RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of about 0.006 mg per mL.

Test solution—Use portions of the solution under test, and pass through a suitable filter having a porosity of 35 µm.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 237-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution* and the *Test solution* as directed for *Procedure:* the retention time of risperidone is about 2.1 minutes, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of $C_{23}H_{27}FN_4O_2$ 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 the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of USP Risperidone RS in 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 75% *(Q)* of the labeled amount of $C_{23}H_{27}FN_4O_2$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩**—**

Mobile phase and *Chromatographic system*—Proceed as directed for *Dissolution*.

Standard solution—Dissolve an accurately weighed quantity of USP Risperidone RS in a suitable volumetric flask, and dilute quantitatively with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.03 mg of risperidone per mL.

Test solution—Transfer one Tablet into a 100-mL volumetric flask, add 50 mL of 0.1 N hydrochloric acid, and shake mechanically for about 30 minutes. Dilute with 0.1 N hydrochloric acid to volume, and mix. Pass a portion of this solution through a suitable filter having a 0.2-µm or finer porosity, and use the filtrate.

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 areas for the risperidone peak. Calculate the quantitiy, in mg, of risperidone ($C_{23}H_{27}FN_4O_2$) in the portion of Tablets taken by the formula:

$$C(r_U / r_S)100$$

in which *C* is the concentration, in mg per mL, of USP Risperidone RS in the *Standard solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Related compounds—

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

Standard solution—Prepare as directed for the *Standard preparation* in the *Assay*.

Diluted sodium hydroxide—To 1 L of water in a beaker, add 0.1 N sodium hydroxide dropwise to obtain a pH of about 8.5.

Diluted hydrogen peroxide—Dilute 1 mL of hydrogen peroxide with water to 500 mL.

Peak identification solution—Suspend 10 mg of USP Risperidone RS in 10 mL of *Diluted sodium hydroxide* in a 100-mL volumetric flask. Store the flask at 90° for 24 hours. Cool the solution to room temperature. Add 10 mL of aqueous *Diluted hydrogen peroxide* to the flask, and store at 90° for an additional two hours. Cool the mixture to room temperature, and dilute with methanol to volume.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay*. Chromatograph about 20 µL of the *Peak identification solution,* record the peak responses as directed for *Procedure,* and identify the peaks using the relative retention times given in *Table 1:* the resolution, *R,* between the *trans-N*-oxide and *cis-N*-oxide is not less than 1.2. [NOTE—The approximate relative retention times given in *Table 1* are for identification purposes only.]