compound A spot, in the chromatogram of the *Sample solution* is more intense than the principal spot in the chromatogram of *Standard solution B* (NMT 1.0%).

SPECIFIC TESTS

- **ACIDITY**
  Sample: 2 g
  Analysis: Digest the *Sample* with 100 mL of water at about 70° for 5 min, cool to about 20°, and filter. Titrate 50 mL of the filtrate with 0.1 N sodium hydroxide VS to a pH of 7.0.
  Acceptance criteria: NMT 0.2 mL is required
- **LOSS ON DRYING ⟨731⟩:** Dry a sample at 105° for 4 h: it loses NMT 1.0% of its weight.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light.
- **LABELING:** Label it to indicate that it is for veterinary use only.
- **USP REFERENCE STANDARDS ⟨11⟩**
  USP Sulfaquinoxaline Related Compound A RS
  N^1,N^2-Diquinoxalin-2-ylsulfanilamide.
  $C_{22}H_{16}N_6SO_2$ 428.50
  USP Sulfaquinoxaline RS

Add the following:

■Sumatriptan Injection

DEFINITION

Sumatriptan Injection is a sterile solution of Sumatriptan Succinate in Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of sumatriptan ($C_{14}H_{21}N_3O_2S$).

IDENTIFICATION

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

ASSAY

- **PROCEDURE**
  Buffer: Add 1.7 mL of butylamine, 0.66 mL of phosphoric acid, and 3.7 g of monobasic sodium phosphate to 900 mL of water. Mix, and adjust with 1 N sodium hydroxide to a pH of 7.5 ± 0.1. Dilute with water to 1000 mL.
  Mobile phase: Acetonitrile and *Buffer* (17:83)
  Diluent: Acetonitrile and water (50:50)
  Standard solution: 0.14 mg/mL of USP Sumatriptan Succinate RS in *Diluent*
  Sample solution: Nominally 0.1 mg/mL of sumatriptan from the Injection in *Diluent*
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 227 nm
  Column: 4.6-mm × 25-cm; 5-µm packing L1
  Flow rate: 1.5 mL/min
  Injection size: 10 µL
  Run time: About 3 times the retention time of sumatriptan
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of sumatriptan ($C_{14}H_{21}N_3O_2S$) in the portion of Injection taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Sumatriptan Succinate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of sumatriptan in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of sumatriptan free base, 295.40
M_{r2} = molecular weight of sumatriptan succinate, 413.49

  Acceptance criteria: 90.0%–110.0%

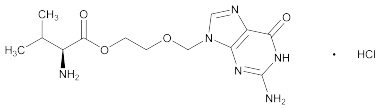
SPECIFIC TESTS

- **pH ⟨791⟩:** 4.2–5.3
- **OSMOLALITY AND OSMOLARITY ⟨785⟩:** 270–330 mOsmol
- **PARTICULATE MATTER IN INJECTIONS ⟨788⟩:** Meets requirements
- **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** It contains NMT 29.2 USP Endotoxin Units/mg of sumatriptan.
- **STERILITY TESTS ⟨71⟩:** Meets the requirements
- **OTHER REQUIREMENTS:** It meets the requirements under *Injections* ⟨1⟩, *Labeling*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in single-dose containers, preferably of Type 1 glass. Store between 2° and 30°, protected from light.
- **USP REFERENCE STANDARDS ⟨11⟩**
  USP Endotoxin RS
  USP Sumatriptan Succinate RS■2S *(USP35)*

Valacyclovir Hydrochloride



$C_{13}H_{20}N_6O_4 \cdot HCl$ 360.80

L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy] ethyl ester, monohydrochloride;
L-Valine, ester with 9-[(2-hydroxyethoxy)methyl]guanine, monohydrochloride [124832-27-5].

DEFINITION

Valacyclovir Hydrochloride contains NLT 95.0% and NMT 102.0% of $C_{13}H_{20}N_6O_4 \cdot HCl$, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩**
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. IDENTIFICATION TESTS—GENERAL,** *Chloride* ⟨**191**⟩
  Sample solution: 50 mg/mL in water
  Acceptance criteria: Meets the requirements

ASSAY

• **PROCEDURE**

Mobile phase: Methanol, water, and perchloric acid (1: 19: 0.1)

Standard solution: 0.5 mg/mL of USP Valacyclovir Hydrochloride RS in 0.05 M hydrochloric acid. [NOTE—USP Valacyclovir Hydrochloride RS contains a detectable quantity of D-valacyclovir.]

Sample solution: 0.5 mg/mL of Valacyclovir Hydrochloride in 0.05 M hydrochloric acid

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4-mm × 15-cm; 5-µm packing L66

Column temperature: 10°

Flow rate: 0.75 mL/min

Injection size: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between valacyclovir hydrochloride and D-valacyclovir

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of valacyclovir hydrochloride ($C_{13}H_{20}N_6O_4 \cdot HCl$) in the portion of Valacyclovir Hydrochloride taken:

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

r_U = peak response of valacyclovir from the *Sample solution*

r_S = peak response of valacyclovir from the *Standard solution*

C_S = concentration of USP Valacyclovir Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Valacyclovir Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.1% on a 2-g sample

• **HEAVY METALS,** *Method II* ⟨**231**⟩**:** NMT 20 ppm

Change to read:

• **LIMIT OF PALLADIUM** (if present)

(See *Plasma Spectrochemistry* ⟨730⟩.)

Diluent: •Water and nitric acid (99.8: 0.2)• (IRA 1-Mar-2012)

Blank solution: *Diluent*

Standard solutions: Dilute with *Diluent* any commercially available standard stock solution of 1 mg/mL of palladium to prepare •the following solutions: 0.03 µg/mL, 0.19 µg/mL, 0.30 µg/mL, 0.38 µg/mL, 0.75 µg/mL, and 1.13 µg/mL of palladium.• (IRA 1-Mar-2012)

Sample solution: •30 mg/mL• (IRA 1-Mar-2012) of Valacyclovir Hydrochloride in *Diluent*

Analytical wavelength: 340.458 nm

Spectrophotometric system: Use a suitable standard inductively coupled plasma–optical emission spectrophotometric system, and construct a calibration curve.

System suitability

Samples: *Blank solution* and *Standard solutions*

Suitability requirements

Relative standard deviation: •NMT 10.0%,• (IRA 1-Mar-2012) *Standard solutions*

Correlation coefficient: •NLT 0.995,• (IRA 1-Mar-2012) *Blank solution* and *Standard solutions*

Analysis

Samples: *Blank solution* and *Sample solution*

Calculate the concentration of palladium using the calibration curve corrected for the emission response of the *Blank solution* and sample weight. Calculate the amount of palladium in the Valacyclovir Hydrochloride taken to prepare the *Sample solution*.

Acceptance criteria: NMT 10 ppm

Change to read:

• **ORGANIC IMPURITIES, PROCEDURE 1** (for related compounds E, F, and G)

Developing solvent: Methylene chloride, methanol, tetrahydrofuran, and ammonia solution (54:34:12:3)

Standard stock solution: •Transfer 5 mg each of USP Valacyclovir Related Compound D RS and USP Valacyclovir Related Compound G RS, 10 mg of USP Valacyclovir Related Compound E RS, and 8.4 mg of USP Valacyclovir Related Compound F RS into a 10-mL volumetric flask.• (IRA 1-Mar-2012) Add 2 mL of water with swirling, followed by 6 mL of alcohol, and sonicate for 20 min. Allow to cool, and dilute with alcohol to volume.

Standard solutions: Transfer 1.0 and 0.5 mL of the *Standard stock solution* into two separate 10-mL volumetric flasks. Dilute the solution in both flasks with alcohol to volume.

Sample solution: Transfer 250 mg of Valacyclovir Hydrochloride into a 5-mL volumetric flask. Add 2 mL of water, and sonicate for 20 min to dissolve. Add alcohol to about 95% volume of the flask. Cool, and dilute with alcohol to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: TLC

Detector: UV, long and short wavelength

Plate: TLC plate coated with a 0.25-mm layer of chromatographic silica gel mixture. Prewash the plate with methanol.

Developing distance: NLT 7 cm from the origin

Application size: 4 µL

Analysis

Samples: *Standard solutions* and *Sample solution*

Develop the plate to the specified distance. Remove the plate from the solvent chamber, and allow to dry. Examine the plate under short-wavelength UV light, and visually estimate the valacyclovir related compounds E and G in the sample using the appropriate standard spots. The chromatograms obtained with the *Standard solutions* each show three clearly separated spots due to valacyclovir related compounds D, E, and G. Spray the plate with 0.01% fluorescamine in ethylene dichloride, and examine the sprayed plate under long-wavelength UV light to estimate the level of valacyclovir related compound F in the sample using the appropriate standard spot. The relative R_F values and limits for each impurity are provided in *Table 1*.

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative R_F Value	Acceptance Criteria, NMT (%)
Valacyclovir hydrochloride	1	—
Valacyclovir related compound D[a]	1.1	—
Valacyclovir related compound E[b]	1.3	0.2
Valacyclovir related compound F[c]	1.8	0.1
Valacyclovir related compound G[d]	1.9	0.05

[a] This impurity is quantitated using *Procedure 2*.
[b] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-[(benzyloxy)carbonyl]-L-valinate.
[c] 2-Hydroxyethyl-L-valinate.
[d] *N*,*N*-Dimethylpyridin-4-amine.

- **ORGANIC IMPURITIES, PROCEDURE 2**

Solution A: 0.3% w/w trifluoroacetic acid solution in water
Solution B: 0.3% w/w trifluoroacetic acid solution in methanol
Diluent: Alcohol and water (1:4)
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	90	10
5	90	10
35	60	40
35.01	90	10
45	90	10

System suitability solution: 0.4 mg/mL of USP Valacyclovir Hydrochloride RS, 0.8 µg/mL of USP Valacyclovir Related Compound C RS, and 1.6 µg/mL of USP Acyclovir Related Compound A RS in *Diluent*
Sample solution: 0.4 mg/mL of Valacyclovir Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 5-µm packing L11
Column temperature: 15°
Flow rate: 0.8 mL/min
Injection size: 10 µL
System suitability
Sample: *System suitability solution*
Resolution: NLT 1.5 between valacyclovir and valacyclovir related compound C, and NLT 1.5 between valacyclovir related compound C and acyclovir related compound A
Tailing factor: NMT 1.5 for the valacyclovir hydrochloride peak
Analysis
Sample: *Sample solution*
Calculate the percentage of each individual impurity in the portion of Valacyclovir Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of any impurity in the *Sample solution*
r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Guanine (near solvent front)[a,b]	0.31	—
Acyclovir[a,c]	0.42	—
Acyclovir alaninate[d]	0.54	0.2
Valacyclovir	1.00	—
Valacyclovir related compound C[e]	1.06	0.3
Acyclovir related compound A[a,f]	1.09	—
Valacyclovir related compound D[g]	1.17	0.5
Acyclovir isoleucinate[h]	1.30	0.2
N-Formyl valacyclovir[i]	1.61	0.8
Guaninyl valacyclovir[j]	1.66	0.2
Bis valacyclovir[k]	2.0	0.3
Any unspecified impurity	—	0.1

[a] This impurity is quantitated by the *Procedure 3* method.
[b] 2-Amino-1*H*-purin-6(9*H*)-one (guanine).
[c] 9-[(2-Hydroxyethoxy)methyl]guanine (acyclovir).
[d] 9-[(2-Hydroxyethoxy)methyl]guanine L-alaninate.
[e] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-methyl-L-valinate.
[f] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl acetate.
[g] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-ethyl-L-valinate.
[h] 9-[(2-Hydroxyethoxy)methyl]guanine L-isoleucinate.
[i] 9-[(2-Hydroxyethoxy)methyl]guanine *N*-formyl-L-valinate.
[j] [N^2-(Guanine-N^2-yl)methyl]-9-[(2-hydroxyethoxy)methyl]guanine L-valinate.
[k] 2,2′-[Methylenebis[imino(6-oxo-1,6-dihydro-9*H*-purine-9,2-diyl)methylene-oxy]]diethyl di(L-valinate).

- **ORGANIC IMPURITIES, PROCEDURE 3**

Mobile phase, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each individual impurity in the portion of Valacyclovir Hydrochloride taken:

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

r_U = peak response of guanine plus acyclovir or acyclovir acetate or D-valacyclovir from the *Sample solution*
r_S = peak response of valacyclovir from the *Standard solution*
C_S = concentration of USP Valacyclovir Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Valacyclovir Hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Guanine and acyclovir[a,b]	0.18	1.51	2.0
Acyclovir related compound A[c]	0.42	1.12	0.2

[a] 2-Amino-1*H*-purin-6(9*H*)-one (guanine).
[b] 9-[(2-Hydroxyethoxy)methyl]guanine (acyclovir).
[c] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl acetate.
[d] D-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy] ethyl ester, monohydrochloride.

Table 4 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
D-Valacyclovir[d]	0.55	1.0	3.0
Valacyclovir	1.0	—	—

[a] 2-Amino-1*H*-purin-6(9*H*)-one (guanine).
[b] 9-[(2-Hydroxyethoxy)methyl]guanine (acyclovir).
[c] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl acetate.
[d] D-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy] ethyl ester, monohydrochloride.

Total organic impurities: NMT 5.0% for the sum of all impurities from *Organic Impurities, Procedures 1*, *2*, and *3*

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** For the anhydrous form: NMT 2.0% (200 mg of sample); if labeled as the hydrous form: 5.0%–11.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at a temperature below 30°.
- **LABELING:** Where it is the hydrous form, the label so indicates.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Acyclovir Related Compound A RS
  [NOTE—USP Acyclovir Related Compound A AS is equivalent.]
  2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy] ethyl acetate.
  $C_{10}H_{13}N_5O_4$ 267.24
  USP Valacyclovir Hydrochloride RS
  USP Valacyclovir Related Compound C RS
  2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy] ethyl *N*-methyl-L-valinate hydrochloride.
  $C_{14}H_{22}N_6O_4 \cdot HCl$ 374.82
  USP Valacyclovir Related Compound D RS
  2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9yl)methoxy] ethyl *N*-ethyl-L-valinate.
  $C_{15}H_{24}N_6O_4$ 352.39
  USP Valacyclovir Related Compound E RS
  2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy] ethyl *N*-benzyloxy)carbonyl]-L-valinate.
  $C_{21}H_{26}N_6O_6$ 458.47
  USP Valacyclovir Related Compound F RS
  2-Hydroxyethyl valinate para-toluenesulfonate salt.
  $C_7H_{15}NO_3 \cdot C_7H_8O_3S$ 333.40
  USP Valacyclovir Related Compound G RS
  N,N-Dimethylpyridin-4-amine.
  $C_7H_{10}N_2$ 122.17

Valsartan and Hydrochlorothiazide Tablets

DEFINITION

Valsartan and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

- **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST** ⟨**201**⟩
  Sample solution: To an amount of ground Tablets, equivalent in weight to a single Tablet, add 2.0 mL of acetone, sonicate for 15 min, and centrifuge.
  Application volume: 2 µL
  Developing solvent system: Ethyl acetate, dehydrated alcohol, and 3.6 M of ammonium hydroxide (8:2:1)
  Analysis: Proceed as directed in the chapter, except develop the plate in a paper-lined chromatographic chamber equilibrated with *Developing solvent system* for 15 min before use. Allow the chromatogram to develop until the solvent front has moved at least 7 cm. After removing the plate and marking the solvent front, dry the plate under a current of warm air. The R_F values of the principal spots from the *Sample solution* correspond to those from the *Standard solution*.
- **B.** 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**
  Diluent: Acetonitrile and water (1:1)
  Solution A: Acetonitrile, water, and trifluoroacetic acid (10: 90: 0.1)
  Solution B: Acetonitrile, water, and trifluoroacetic acid (90: 10: 0.1)
  Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
25	10	90
27	90	10
40	90	10

Standard solution: Transfer 12.5 mg of USP Hydrochlorothiazide RS to a 200-mL volumetric flask, and add 12.5*J* mg of USP Valsartan RS, *J* being the ratio of the labeled amount, in mg, of valsartan to the labeled amount, in mg, of hydrochlorothiazide per Tablet. Add 100 mL of *Diluent*, sonicate for 15 min, dilute with *Diluent* to volume, and mix. Transfer 25.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Dilute with *Diluent* to obtain a solution having a concentration of 0.2 mg/mL of USP Valsartan RS in *Diluent*.
Sample stock solution: To the equivalent of 62.5 mg of hydrochlorothiazide from a number of Tablets add 5 mL of water, and allow to stand for 5 min. Then add 100 mL of *Diluent*, sonicate for 15 min, and shake for 30 min. Dilute with *Diluent* to 250 mL, and centrifuge a portion of this solution at 3000 rpm. Dilute 25.0 mL of the clear supernatant with *Diluent* to 200.0 mL.
Sample solution: 0.2 mg/mL of valsartan, from *Sample stock solution* in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 265 nm
Column: 3.0-mm × 12.5-cm; 5-µm packing L1
Flow rate: 0.4 mL/min
Injection size: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets 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 the appropriate USP Reference Standard in the *Standard solution* (mg/mL)