Impurity Table

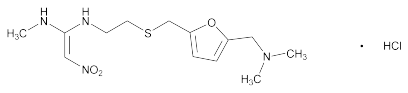
Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%) for 1.25-mg Capsules	Acceptance Criteria, NMT (%) for 2.5-mg Capsules	Acceptance Criteria, NMT (%) for 5-mg and 10-mg Capsules
Ramipril diacid	0.24	0.41	1.0	1.0	1.0
Ramipril related compound A[a]	0.72	—	—	—	—
Ramipril diacid impurity[a]	0.85	—	—	—	—
Ramipril	1	—	—	—	—
Ramipril related compound B[a]	1.31	—	—	—	—
Ramipril related compound C[a]	1.68	—	—	—	—
Ramipril related compound D[b]	1.84	1	8.0	5.5	5.0
Any other individual unspecifed degradant	—	—	0.2	0.2	0.2

[a] Disregard this impurity as it is process related and is controlled in the drug substance.
[b] Ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate (Ramipril diketopiperazine).

Acceptance criteria
Individual impurities: See *Impurity Table*.
Total impurities: NMT 8.0% for Capsule strength 1.25 mg, NMT 7.0% for Capsule strength 2.5 mg, and NMT 6.0% for Capsule strengths 5 mg and 10 mg. [NOTE—Total impurities include the sum of individual specified and unspecified degradants. Disregard any peak below 0.1%.]

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Ramipril RS
  USP Ramipril Related Compound A RS
  (2*S*,3a*S*,6a*S*)-1-[(*S*)2-[[(*S*)1-(Methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid.
  $C_{22}H_{30}N_2O_5$ 402.48

Ranitidine Hydrochloride



$C_{13}H_{22}N_4O_3S \cdot HCl$ 350.87
1,1-Ethenediamine, *N*-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]-methyl]thio]ethyl]-*N'*-methyl-2-nitro-, monohydrochloride.
N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N'*-methyl-2-nitro-1,1-ethenediamine, hydrochloride [66357-59-3].

» Ranitidine Hydrochloride contains not less than 97.5 percent and not more than 102.0 percent of $C_{13}H_{22}N_4O_3S \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩**—**
USP Ranitidine Hydrochloride RS
USP Ranitidine Resolution Mixture RS
It is a mixture of ranitidine hydrochloride and four related impurities: ranitidine-*N*-oxide, ranitidine complex nitroacetamide, ranitidine diamine hemifumarate, and ranitidine amino alcohol hemifumarate.
Ranitidine-N-oxide: N,N-dimethyl[5-[[[2-[[1-(methylamino)-2-nitroethenyl]amino]ethyl]sulphanyl]methyl]furan-2-yl]methanamine *N*-oxide.
Ranitidine complex nitroacetamide: N-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-2-nitroacetamide.
Ranitidine diamine hemifumarate (related compound A): 5-[[(2-aminoethyl)thio]methyl]-*N,N*-dimethyl-2-furanmethanamine, hemifumarate salt.
Ranitidine amino alcohol hemifumarate: [5-[(dimethylamino)methyl]furan-2-yl]methanol.

Identification—
A: *Infrared Absorption* ⟨197M⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 10 µg per mL.
Medium: water.
Absorptivities at 229 nm and 315 nm, calculated on the dried basis, do not differ by more than 3.0%.
C: A solution of it meets the requirements of the tests for *Chloride* ⟨191⟩.

pH ⟨791⟩: between 4.5 and 6.0, in a solution (1 in 100).

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 3 hours: it loses not more than 0.75% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Chromatographic purity—
Diluent, Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay*.
Standard solution—Prepare as directed for *Standard preparation* in the *Assay*.
Test solution—Prepare as directed for *Assay preparation* in the *Assay*.
Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify the ranitidine peak and the peaks due to impurities and degradation products listed in the table below.

Name	Relative Retention Time
Ranitidine simple nitroacetamide[1]	0.14
Ranitidine oxime[2]	0.21
Ranitidine amino alcohol[3]	0.45
Ranitidine diamine[4]	0.57
Ranitidine *S*-oxide[5]	0.64
Ranitidine *N*-oxide[6]	0.72
Ranitidine complex nitroacetamide[7]	0.84
Ranitidine formaldehyde adduct[8]	1.36
Ranitidine *bis*-compound[9]	1.75

[1]*N*-Methyl-2-nitroacetamide.

[2]3-(Methylamino)-5,6-dihydro-2*H*-1,4-thiazin-2-one oxime.

[3]{5-[(Dimethylamino)methyl]furan-2-yl}methanol.

[4]5-{[(2-Aminoethyl)thio]methyl}-*N,N*-dimethyl-2-furanmethanamine (ranitidine related compound A).

[5]*N*-{2-[({5-[(Dimethylamino)methyl]-2-furanyl}methyl)sulfinyl]ethyl}-*N'*-methyl-2-nitro-1,1-ethenediamine (ranitidine related compound C).

[6]*N,N*-Dimethyl(5-{[(2-{[1-(methylamino)-2-nitroethenyl]amino}ethyl) sulphanyl]methyl}furan-2-yl)methanamine *N*-oxide.

[7]*N*-{2-[({5-[(Dimethylamino)methyl]furan-2-yl}methyl)sulphanyl]ethyl}-2-nitroacetamide.

[8]2,2′-Methylenebis(*N*-{2-[({5-[(dimethylamino)methyl]furan-2-yl}methyl)-sulphanyl]ethyl}-*N'*-methyl-2-nitroethene-1,1-diamine).

[9]*N,N'*-bis{2-[({5-[(Dimethylamino)methyl]-2-furanyl}methyl)thio]ethyl}-2-nitro-1,1-ethenediamine (ranitidine related compound B).

Measure the responses for the major peaks, and calculate the percentage of each impurity in the portion of Ranitidine Hydrochloride taken by the formula:

$$100CV/W(r_i / r_S)$$

in which *C* is the concentration, in mg per mL, of ranitidine hydrochloride in the *Standard solution; V* is the volume, in mL, of the *Test solution; W* is the weight, in mg, of Ranitidine Hydrochloride taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the ranitidine peak response obtained from the *Standard solution:* not more than 0.3% of ranitidine bis-compound is found, not more than 0.1% of any other single impurity is found, and not more than 0.5% of total impurities is found. The reporting level for impurities is 0.05%.

Assay—

Phosphate buffer—Place approximately 1900 mL of water in a 2.0-L volumetric flask, accurately add 6.8 mL of phosphoric acid, and mix. Accurately add 8.6 mL of 50% sodium hydroxide solution, and dilute with water to volume. If necessary, adjust with 50% sodium hydroxide solution or phosphoric acid to a pH of 7.1, and filter.

Solution A—Prepare a mixture of *Phosphate buffer* and acetonitrile (98:2).

Solution B—Prepare a mixture of *Phosphate buffer* and acetonitrile (78:22).

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—Use *Solution A.*

Standard preparation—Dissolve an accurately weighed quantity of USP Ranitidine Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 0.125 mg of ranitidine hydrochloride per mL.

Resolution solution—Transfer about 1.3 mg of USP Ranitidine Resolution Mixture RS to a 10-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume. [NOTE—USP Ranitidine Resolution Mixture RS contains ranitidine hydrochloride and four related impurities: ranitidine amino alcohol hemifumarate, ranitidine diamine hemifumarate, ranitidine *N*-oxide, and ranitidine complex nitroacetamide.]

Assay preparation—Transfer about 25 mg of Ranitidine Hydrochloride, accurately weighed, to a 200-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 230-nm detector and a 4.6-mm × 10-cm column containing 3.5-µm packing L1 that is stable from pH 1 to 12. 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
0–10	100→0	0→100	linear gradient
10–15	0	100	isocratic
15–16	0→100	100→0	linear gradient
16–20	100	0	re-equilibration

Chromatograph the *Resolution solution,* and identify the peaks using the table of impurities and degradation products (found above): the resolution, *R,* between the peaks for ranitidine *N*-oxide and ranitidine complex nitroacetamide is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of $C_{13}H_{22}N_4O_3S \cdot HCl$ in the portion of Ranitidine Hydrochloride 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 ranitidine hydrochloride 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.

Ranitidine Injection

» Ranitidine Injection is a sterile solution of Ranitidine Hydrochloride in Water for Injection. It contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ranitidine ($C_{13}H_{22}N_4O_3S$).

Packaging and storage—Preserve in single-dose or in multiple-dose containers of Type I glass, protected from light. Store below 30°. Do not freeze.

Labeling—Label Injection to state both the content of the active moiety and the content of the salt used in formulating the article.

USP Reference standards ⟨11⟩**—**
USP Ranitidine Hydrochloride RS
USP Ranitidine Related Compound A RS
5-[[(2-Aminoethyl)thio]methyl]-*N,N*-dimethyl-2-furanmethanamine, hemifumarate salt.
USP Ranitidine Related Compound C RS
N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]sulfinyl]ethyl]-*N*-methyl-2-nitro-1,1-ethenediamine.

Identification—

A: The R_F value of the principal spot observed in the chromatogram of the *Test preparation* obtained as directed in the *Chromatographic purity* test corresponds to that obtained from the *Standard preparation.*