

Zolpidem Tartrate Tablets

DEFINITION

Zolpidem Tartrate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$.

IDENTIFICATION

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

Buffer: 3.4 g/L of monobasic potassium phosphate in water, adjusted with ammonium hydroxide to a pH of 5.5

Mobile phase: Acetonitrile, methanol, and *Buffer* (30:20:50)

Standard stock solution: 0.8 mg/mL of USP Zolpidem Tartrate RS in 0.01 N hydrochloric acid TS

Standard solution: 0.16 mg/mL of USP Zolpidem

Tartrate RS in *Mobile phase*, from the *Standard stock solution*
Sample stock solution: Nominally 0.4 mg/mL of zolpidem tartrate from NLT 20 Tablets prepared as follows. Transfer the Tablets to a suitable volumetric flask and add 40% of the flask volume of 0.125 N hydrochloric acid TS. Mix well until the Tablets disintegrate, and add 50% of the flask volume of *Mobile phase*. Dilute with water to volume, and stir for 30 min using a magnetic stirrer. Allow solid particles to settle, and pass the supernatant through a suitable filter.¹

Sample solution: Nominally 0.16 mg/mL of zolpidem tartrate in *Mobile phase*, from the *Sample stock solution*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.

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

Flow rate: 1.2 mL/min

Injection volume: 10 μL

Run time: NLT 2.5 times the retention time of zolpidem tartrate

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 3.0 for zolpidem

Relative standard deviation: NMT 2.0% for zolpidem

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ 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 USP Zolpidem Tartrate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of zolpidem tartrate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

¹ The Whatman #40 filter or equivalent may be suitable.

PERFORMANCE TESTS

Change to read:

DISSOLUTION <711>

Test 1

Medium: 0.01 N hydrochloric acid TS; 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 15 min

[▲]Perform the analysis by using either the *Spectrophotometric procedure* or the *Chromatographic procedure*.

Spectrophotometric procedure [▲] (USP 1-Aug-2020)

Standard solution: (L/1000) mg/mL of USP Zolpidem Tartrate RS in *Medium*, where L is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

Instrumental conditions

Mode: UV

Analytical wavelength: 295 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Chromatographic procedure

Solution A: 5.6 g/L of phosphoric acid in water, adjusted with triethylamine to a pH of 5.5

Mobile phase: Acetonitrile, methanol, and *Solution A* (18:23:59)

Standard solution: (L/900) mg/mL of USP Zolpidem Tartrate RS in *Medium*, where L is the label claim of zolpidem tartrate in mg/Tablet. Sonicate as needed.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 15-cm; 4-μm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 20 μL

Run time: NLT 1.5 times the retention time of zolpidem tartrate

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 zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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- C_S = concentration of USP Zolpidem Tartrate RS in the Standard solution (mg/mL)
 L = label claim (mg/Tablet)
 V = volume of Medium, 900 mL (USP 1-Aug-2020)

Tolerances: NLT 80% (Q) of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: 0.1 N hydrochloric acid VS; 900 mL

Apparatus 2: 50 rpm

Time: 20 min

Standard solution: $(L/900)$ mg/mL of USP Zolpidem Tartrate RS in Medium, where L is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter.

Instrumental conditions

Mode: UV

Analytical wavelength: 295 nm

Blank: Medium

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

- A_U = absorbance of the Sample solution
 A_S = absorbance of the Standard solution
 C_S = concentration of USP Zolpidem Tartrate RS in the Standard solution (mg/mL)
 L = label claim (mg/Tablet)
 V = volume of Medium, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.

Medium: 0.01 N hydrochloric acid TS; 900 mL

Apparatus 2: 50 rpm

Time: 15 min

Standard solution: $(L/900)$ mg/mL of USP Zolpidem Tartrate RS in Medium, where L is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size.

Instrumental conditions

Mode: UV

Analytical wavelength: 295 nm

Blank: Medium

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

- A_U = absorbance of the Sample solution
 A_S = absorbance of the Standard solution
 C_S = concentration of USP Zolpidem Tartrate RS in the Standard solution (mg/mL)
 L = label claim (mg/Tablet)
 V = volume of Medium, 900 mL

Tolerances: NLT 85% (Q) of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

IMPURITIES

• ORGANIC IMPURITIES

Solution A: 3.3 mL/L of phosphoric acid in water, adjusted with triethylamine to a pH of 6.0

Solution B: Acetonitrile

Solution C: Methanol

Mobile phase: See Table 1.

Table 1

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	76	14	10
35.0	48	16	36
36.5	48	16	36
37.5	76	14	10
42.0	76	14	10

Diluent: Solution B, Solution C, and Solution A (15:10:75)

System suitability solution: 0.5 mg/mL of USP Zolpidem Tartrate RS and 0.0008 mg/mL of USP Zolpidem Related Compound A RS in Diluent

Standard solution: 0.005 mg/mL of USP Zolpidem Tartrate RS in Diluent

Sample solution: Nominally equivalent to 0.5 mg/mL of zolpidem tartrate in Diluent from NLT 10 Tablets, prepared as follows. Transfer the Tablets to a suitable volumetric flask, add 70% of the flask volume of Diluent, and stir for 30 min. Dilute with Diluent to volume. Centrifuge a portion of the solution and use the clear supernatant.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm $\times$ 15-cm; 4- μ m packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 μ L

System suitability

Samples: System suitability solution and Standard solution

Suitability requirements

Resolution: NLT 2.0 between zolpidem and zolpidem related compound A, System suitability solution

Relative standard deviation: NMT 5.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of each degradation product in the portion of Tablets taken:

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

- r_U = peak response of each degradation product from the Sample solution
 r_S = peak response of zolpidem from the Standard solution
 C_S = concentration of USP Zolpidem Tartrate RS in the Standard solution (mg/mL)
 C_U = nominal concentration of zolpidem tartrate in the Sample solution (mg/mL)
 F = relative response factor (see Table 2)

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tolyloyl propionic acid ^{a, b}	0.15	—	—
Zolpidem acid ^c	0.18	1.0	0.3
Tolyloyl propionamide ^{b, d}	0.54	—	—
Tolyloyl acrylamide ^{b, e}	0.65	—	—
Zolpidem related compound B ^f	0.83	1.1	0.3
Zolpidem related compound A	0.91	1.1	0.20
Zolpidem	1.0	—	—
Tolyloyl bromopropionamide ^{b, g}	1.14	—	—
Zolpidem related compound C ^h	1.20	1.1	0.3
Zolpidem 3-carbaldehyde ⁱ	1.65	1.4	0.3
Any individual unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	0.5

^a 4-Oxo-4-(*p*-tolyl)butanoic acid.

^b Process impurities related to specific manufacturing process of the drug substance; included for peak identification purposes only and are not to be reported or included in the total degradation products.

^c 2-(6-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetic acid.

^d *N,N*-Dimethyl-4-oxo-4-(*p*-tolyl)butanamide.

^e *N,N*-Dimethyl-4-oxo-4-(*p*-tolyl)but-2-enamide.

^f *N,N*-Dimethyl-2-(6-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)-2-oxoacetamide.

^g 3-Bromo-*N,N*-dimethyl-4-oxo-4-(*p*-tolyl)butanamide.

^h 4-Methyl-*N*-(5-methylpyridin-2-yl)benzamide.

ⁱ 6-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridine-3-carbaldehyde.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** (11)
 - USP Zolpidem Tartrate RS
 - USP Zolpidem Related Compound A RS
 - N,N*-Dimethyl-2-(7-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetamide.
 - C₁₉H₂₁N₃O 307.39

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Natrium BPFi; lakukan pengeringan pada suhu 105° selama 4 jam sebelum digunakan. Simpan dalam wadah tertutup rapat.

Identifikasi

A. Isi kapsul menunjukkan reaksi seperti yang tertera pada *Identifikasi cara A* dalam *Fenitoin Natrium*.

B. Isi kapsul menunjukkan reaksi nyala api *Natrium* seperti yang tertera pada *Uji Identifikasi Umum* <291>.

Disolusi <1231>

Media disolusi: 900 mL air

Alat tipe 1: 50 rpm

Waktu: 30 menit

Prosedur Lakukan penetapan jumlah $C_{15}H_{11}N_2NaO_2$ yang terlarut dengan mengukur serapan alikot, jika perlu encerkan dengan *Media disolusi*, dan larutan baku *Fenitoin Natrium BPFi* yang sudah diketahui kadarnya dalam media yang sama pada panjang gelombang serapan maksimum lebih kurang 258 nm.

Toleransi Dalam waktu 30 menit harus larut tidak kurang dari 85% (Q) $C_{15}H_{11}N_2NaO_2$, dari jumlah yang tertera pada etiket.

Keseragaman sediaan <911> Memenuhi syarat.

Prosedur untuk keseragaman kandungan

Dapar, Fase gerak, Sistem kromatografi Lakukan seperti yang tertera pada *Penetapan kadar*.

Larutan baku Larutkan *Fenitoin BPFi* dalam *metanol P*, dan encerkan dengan *Fase gerak* hingga kadar lebih kurang 0,5 mg per mL.

Larutan uji Masukkan 1 buah kapsul utuh atau yang telah dibuka beserta isi kapsul ke dalam wadah yang sesuai, tambahkan 15 mL *metanol P* dan panaskan di atas tangas air dengan pengocok pada suhu 37° selama 30 menit. Sonikasi selama 60 menit sambil sesekali dikocok. Encerkan dengan *metanol P* sampai tanda. Jika perlu encerkan dengan *Fase gerak* hingga kadar lebih kurang 0,5 mg per mL.

Penetapan kadar Lakukan penetapan dengan cara *Kromatografi cair kinerja tinggi* seperti yang tertera pada *Kromatografi* <931>.

Dapar Buat *dapar kalium fosfat monobasa 0,05 M*, atur pH hingga 3,5 dengan penambahan *asam fosfat P*.

Fase gerak Buat campuran *metanol P* dan *Dapar* (55:45). Saring dan awaudarakan. Jika perlu lakukan penyesuaian menurut *Kesesuaian sistem* seperti yang tertera pada *Kromatografi* <931>.

Larutan baku Timbang sejumlah *Fenitoin BPFi* larutkan dan encerkan dengan *Fase gerak* hingga kadar lebih kurang 0,6 mg per mL. [Catatan Larutkan sejumlah *Fenitoin BPFi* yang diperlukan dengan sedikit *metanol P* sebelum diencerkan dengan *Fase gerak*.]

Larutan uji persediaan Masukkan isi dari 10 kapsul ke dalam labu tentukur 250-mL. Tambahkan 150 mL *metanol P* dan sonikasi selama 20 menit. Dinginkan hingga suhu ruang dan encerkan dengan *metanol P* sampai tanda.

Larutan uji Encerkan sejumlah *Larutan uji persediaan* dengan *Fase gerak* hingga kadar lebih kurang 0,6 mg per mL.

Sistem kromatografi Lakukan seperti yang tertera pada *Kromatografi* <931>. Kromatograf cair kinerja tinggi dilengkapi dengan detektor 229 nm dan kolom 4,6 mm x 25 cm berisi bahan pengisi *L1*. Laju alir lebih kurang 1 mL per menit. Lakukan kromatografi terhadap *Larutan baku*, rekam kromatogram dan ukur respons puncak seperti yang tertera pada *Prosedur*. Efisiensi kolom tidak kurang dari 3000 lempeng teoritis; faktor ikutan tidak lebih dari 2,0 dan simpangan baku relatif tidak lebih dari 2,0%.

Prosedur Suntikkan secara terpisah sejumlah volume sama (lebih kurang 10 µL) *Larutan baku* dan *Larutan uji* ke dalam kromatograf, rekam kromatogram dan ukur respons puncak utama. Hitung persentase fenitoin natrium, $C_{15}H_{11}N_2NaO_2$, dalam kapsul dengan rumus:

$$\left(\frac{r_U}{r_S}\right) \left(\frac{C_S}{C_U}\right) \left(\frac{274,25}{252,27}\right) 100$$

r_U dan r_S berturut-turut adalah respons puncak dari *Larutan uji* dan *Larutan baku*; C_S adalah kadar *Fenitoin BPFi* dalam mg per mL *Larutan baku*; C_U adalah kadar fenitoin dalam mg per mL *Larutan uji* berdasarkan jumlah yang tertera pada etiket; 274,25 dan 252,27 berturut-turut adalah bobot molekul fenitoin natrium dan fenitoin.

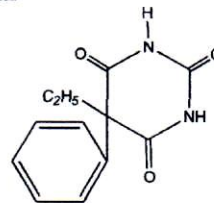
Wadah dan penyimpanan Dalam wadah tertutup rapat.

Penandaan Pada etiket tertera dengan jelas "Tidak untuk dosis sehari satu kali". Dicetak dibawah nama obat dalam cetak tebal dan warna kontras atau dalam kotak.

FENOBARBITAL

Luminal

Phenobarbital



Asam 5-etil-5-fenilbarbiturat [50-06-6]
 $C_{12}H_{12}N_2O_3$

BM 232,24

Fenobarbital mengandung tidak kurang dari 98,0% dan tidak lebih dari 101,0% $C_{12}H_{12}N_2O_3$, dihitung terhadap zat kering.

Pemerian Hablur kecil atau serbuk hablur putih berkilat; tidak berbau; tidak berasa; dapat terjadi polimorfisma. Stabil di udara; pH larutan jenuh lebih kurang 5.

Kelarutan Sangat sukar larut dalam air; larut dalam etanol, eter, larutan alkali hidroksida dan alkali karbonat; agak sukar larut dalam kloroform.

Baku pembanding *Fenobarbital BPFI*; lakukan pengeringan pada suhu 105° selama 2 jam sebelum digunakan.

Identifikasi

A. Spektrum serapan inframerah zat yang didispersikan dalam *kalium bromida P* menunjukkan maksimum hanya pada bilangan gelombang yang sama seperti pada *Fenobarbital BPFI*. Jika ada perbedaan, larutkan masing-masing sejumlah zat dan sejumlah *Fenobarbital BPFI* dalam pelarut yang sesuai, uapkan masing-masing larutan sampai kering dan ulangi pengujian menggunakan residu.

B. Waktu retensi puncak utama *Larutan uji* sesuai dengan *Larutan baku*, keduanya relatif terhadap baku internal yang diperoleh pada *Penetapan kadar*.

Jarak lebur <1021> Antara 174° dan 178°, tetapi rentang antara awal dan akhir melebur tidak lebih dari 2°.

Susut pengeringan <1121> Tidak lebih dari 1,0%; lakukan pengeringan pada suhu 105° selama 2 jam.

Sisa pemijaran <301> Tidak lebih dari 0,15%.

Penetapan kadar Lakukan *Kromatografi cair kinerja tinggi* seperti tertera pada *Kromatografi* <931>.

Dapar pH 4,5 Larutkan lebih kurang 6,6 g *natrium asetat trihidrat P* dan 3,0 mL *asam asetat glasial P* dalam 1000 mL air; jika perlu, atur pH hingga $4,5 \pm 0,1$ dengan *asam asetat glasial P*.

Fase gerak Buat campuran *Dapar pH 4,5-metanol P* (3 : 2), saring dan awaudarkan. Jika perlu lakukan penyesuaian menurut *Kesesuaian sistem* seperti tertera pada *Kromatografi* <931>.

Larutan baku internal Timbang saksama sejumlah kafein, larutkan dalam campuran *metanol P-Dapar pH 4,5* (1 : 1) hingga kadar lebih kurang 125 µg per mL.

Larutan baku Timbang saksama lebih kurang 20 mg *Fenobarbital BPFI*, larutkan dalam 15,0 mL *Larutan baku internal*. Jika perlu sonikasi.

Larutan uji Timbang saksama lebih kurang 20 mg, masukkan ke dalam labu Erlenmeyer, tambahkan 15,0 mL *Larutan baku internal*, sonikasi selama 15

menit. Saring dengan penyaring membran dengan porositas 0,5 µm atau lebih halus, sebelum digunakan.

Sistem kromatografi Lakukan seperti tertera pada *Kromatografi* <931>. Kromatograf cair kinerja tinggi dilengkapi dengan detektor 254 nm dan kolom 4 mm x 25 cm berisi bahan pengisi *L1*. Laju alir lebih kurang 2 mL per menit. Lakukan kromatografi terhadap *Larutan baku*, rekam kromatogram dan ukur respons puncak seperti tertera pada *Prosedur*: resolusi, *R*, antara puncak analit dan puncak baku internal tidak kurang dari 1,2, faktor ikutan puncak analit dan puncak baku internal tidak lebih besar dari 2,0 dan simpangan baku relatif pada penyuntikan ulang tidak lebih dari 2,0 %.

Prosedur Suntikkan secara terpisah sejumlah volume sama (lebih kurang 10 µL) *Larutan baku* dan *Larutan uji* ke dalam kromatograf, ukur respons puncak utama. Waktu retensi relatif kafein dan fenobarbital berturut-turut adalah lebih kurang 0,6 dan 1,0. Hitung jumlah dalam mg fenobarbital, $C_{12}H_{12}N_2O_3$, dalam zat yang digunakan dengan rumus:

$$W \left(\frac{R_U}{R_S} \right)$$

W adalah bobot *Fenobarbital BPFI* dalam mg dalam *Larutan baku*; R_U dan R_S berturut-turut adalah perbandingan respons puncak *Larutan uji* dan *larutan baku*.

Wadah dan penyimpanan Dalam wadah tertutup baik.

TABLET FENOBARBITAL

Tablet Luminal

Phenobarbital Tablet

Tablet fenobarbital mengandung fenobarbital, $C_{12}H_{12}N_2O_3$, tidak kurang dari 90,0% dan tidak lebih dari 110,0% dari jumlah yang tertera dalam etiket.

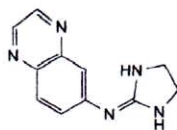
Baku pembanding *Fenobarbital BPFI*; lakukan pengeringan pada suhu 105° selama 2 jam sebelum digunakan.

Identifikasi

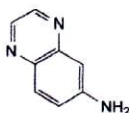
A. Gerus halus sejumlah serbuk tablet setara dengan lebih kurang 60 mg fenobarbital, dengan 50 mL *kloroform P*, saring. Uapkan filtrat jernih hingga kering dan keringkan pada suhu 105° selama 2 jam; residu memenuhi *Identifikasi A* seperti tertera pada *Fenobarbital*.

B. Waktu retensi relatif puncak utama *Larutan uji* sesuai dengan *Larutan baku*, keduanya relatif terhadap baku internal yang diperoleh pada *Penetapan kadar*.

Ry 26/26

A. *N*-(imidazolidin-2-ylidene)quinoxalin-6-amine,

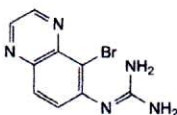
B. 5-bromoquinoxalin-6-amine,



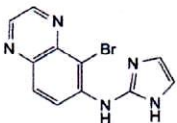
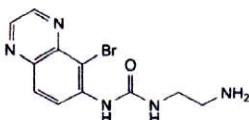
C. quinoxalin-6-amine,



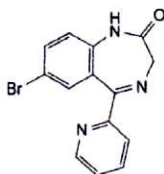
D. 1-(5-bromoquinoxalin-6-yl)thiourea,



E. 2-(5-bromoquinoxalin-6-yl)guanidine,

F. 5-bromo-*N*-(1*H*-imidazol-2-yl)quinoxalin-6-amine,

G. 1-(2-aminoethyl)-3-(5-bromoquinoxalin-6-yl)urea.

**BROMAZEPAM****Bromazepamum**

$C_{14}H_{10}BrN_3O$
[1812-30-2]

M_r 316.2

DEFINITION

7-Bromo-5-(pyridin-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or yellowish, crystalline powder.

Solubility: practically insoluble in water, slightly soluble or sparingly soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison: bromazepam CRS.

TESTS

Related substances. Liquid chromatography (2.2.29). Prepare the solutions immediately before use.

Solvent mixture. Mix 1 volume of acetonitrile R and 8 volumes of methanol R.

Test solution. Dissolve 10.0 mg of the substance to be examined in 9 mL of the solvent mixture. Dilute to 20.0 mL with an 11.33 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 7.0 with a 100 g/L solution of potassium hydroxide R.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of bromazepam for system suitability A CRS (containing impurities A and C) in 5 mL of the solvent mixture. Dilute to 10 mL with an 11.33 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 7.0 with a 100 g/L solution of potassium hydroxide R.

Column:

- size: $l = 0.15$ m, $\varnothing = 4.6$ mm;
- stationary phase: end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R (3.5 μ m);
- temperature: 50 °C.

Mobile phase: mix 5 volumes of acetonitrile for chromatography R, 45 volumes of methanol R1 and 50 volumes of an 11.33 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 7.0 with a 100 g/L solution of potassium hydroxide R.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 235 nm.

Injection: 20 μ L.

Run time: 4 times the retention time of bromazepam.

Identification of impurities: use the chromatogram supplied with bromazepam for system suitability A CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention with reference to bromazepam (retention time = about 5 min): impurity A = about 1.5; impurity C = about 1.6.

System suitability: reference solution (b):

- resolution: minimum 1.2 between the peaks due to impurities A and C.

Calculation of percentage contents:

- for each impurity, use the concentration of bromazepam in reference solution (a).

Limits:

- unspecified impurities: for each impurity, maximum 0.10 per cent;
- total: maximum 0.2 per cent;
- reporting threshold: 0.05 per cent.

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Handwritten signature/initials

Loss on drying (2.2.32): maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 4 h.

Sulfated ash (2.4.14): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 20 mL of *anhydrous acetic acid* R. Add 50 mL of *acetic anhydride* R. Titrate with 0.1 M *perchloric acid*, determining the end-point potentiometrically (2.2.20).

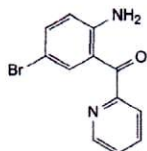
1 mL of 0.1 M *perchloric acid* is equivalent to 31.62 mg of $C_{14}H_{16}BrN_3O$.

STORAGE

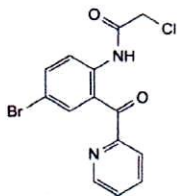
Protected from light.

IMPURITIES

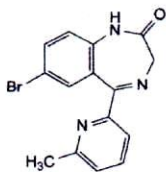
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use* (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. *Control of impurities in substances for pharmaceutical use*): A, B, C, D, E.



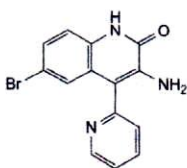
A. (2-amino-5-bromophenyl)(pyridin-2-yl)methanone,



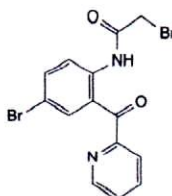
B. N-[4-bromo-2-(pyridine-2-carbonyl)phenyl]-2-chloroacetamide,



C. 7-bromo-5-(6-methylpyridin-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one,



D. 3-amino-6-bromo-4-(pyridin-2-yl)quinolin-2(1H)-one,



E. 2-bromo-N-[4-bromo-2-(pyridine-2-carbonyl)phenyl]acetamide.



BROMHEXINE HYDROCHLORIDE

Bromhexini hydrochloridum



$C_{14}H_{21}Br_2ClN_2$
[611-75-6]

M_r 412.6

DEFINITION

2,4-Dibromo-6-[[cyclohexyl(methyl)amino]methyl]aniline hydrochloride.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very slightly soluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison: bromhexine hydrochloride CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol* R, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution. Dissolve 10 mg of the substance to be examined in *methanol* R and dilute to 5.0 mL with the same solvent.

Reference solution. Dissolve 10 mg of *bromhexine hydrochloride* CRS in *methanol* R and dilute to 5.0 mL with the same solvent.

Plate: TLC silica gel F_{254} plate R.

Mobile phase: concentrated ammonia R, 2-propanol R, acetone R (1:29:70 V/V/V).

Application: 2 μ L.

Development: over 3/4 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.