भारतीय भेषज संहिता आयोग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय, भारत सरकार
सैक्टर-२३, राज नगर,
गाजियाबाद-२०१००२, उत्तर प्रदेश, भारत.

INDIAN PHARMACOPOEIA COMMISSION
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar,
Ghaziabad-201 002 (U.P.), INDIA.

Dt: 01.12.2022

CORRIGENDUM-I

Sub:- Monographs/Draft Monographs for Tendered Impurities- reg.

In respect of **Tender No. IPC/5533/2022-23, Dated. 16.11.2022** regarding Supply of Pharmaceutical Impurities at IPC, Ghaziabad, the Monographs/ Draft Monograph for some of the Tendered Impurities are annexed herewith for the ready reference.

Bidders are advised to comply the same and all other content of tender document including terms and conditions remain unaltered.

Note: Prospective Bidders are also advised to check our website regularly prior to closing date and time for submission of bids.

Sd/-
Stores Officer (I/C)
For Secretary-cum-Scientific Director

Amiodarone Hydrochloride. Page 1437

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *acetonitrile* and *water.*

Test solution. Dissolve 50 mg of the substance under examination in 10.0 ml of the solvent mixture.

Reference solution (a). A solution containing 0.02 per cent w/v each of, *amiodarone impurity D IPRS, amiodarone impurity E IPRS* and *amiodarone hydrochloride IPRS* in *methanol.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 30 volumes of buffer solution prepared by diluting 3.0 ml of *glacial acetic acid* with 800 ml of *water*, adjusted to pH 4.9 with *dilute ammonia* and dilute to 1000 ml with *water*, 30 volumes of *methanol* and 40 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 10 µl.

Name	Relative retention time
Amiodarone impurity A[1]	0.26
Amiodarone impurity D[2]	0.29
Amiodarone impurity E[3]	0.37
Amiodarone impurity B[4]	0.49
Amiodarone impurity C[5]	0.55
Amiodarone impurity G[6]	0.62
Amiodarone impurity F[7]	0.69
Amiodarone	1.00

[1](2-Butylbenzofuran-3-yl){4-[2-(diethylamino)ethoxy]phenyl}methanone,
[2](2-Butylbenzofuran-3-yl)(4-hydroxy-3,5-diiodophenyl)methanone,
[3](2-Butylbenzofuran-3-yl)(4-hydroxyphenyl)methanone,
[4](2-Butylbenzofuran-3-yl){4-[2-(ethylamino)ethoxy]-3,5-diiodophenyl}methanone,
[5](2-Butylbenzofuran-3-yl){4-[2-(diethylamino)ethoxy]-3-iodophenyl}methanone,
[6] [2-[(1RS)-1-Methoxybutyl]benzofuran-3-yl][4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone,
[7](2-Butylbenzofuran-3-yl)(4-hydroxy-3-iodophenyl)methanone.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to amiodarone impurity D and amiodarone impurity E is not less than 3.5 in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. Run the chromatogram twice the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any secondary peaks corresponding to amiodarone impurity A, amiodarone impurity D, amiodarone impurity E, amiodarone impurity B, amiodarone impurity C, amiodarone impurity G and amiodarone impurity F, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with the reference solution (b) (0.05per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *acetonitrile* and *water.*

Test solution. Dissolve 50 mg of the substance under examination in 100.0 ml in the *methanol.* Dilute 2.0 ml of this solution to10 .0 ml with solvent mixture.

Reference solution. A 0.05 per cent w/v solution of *amiodarone hydrochloride IPRS* in the *methanol.* Dilute 2.0 ml of this solution to10 .0 ml with solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 3.9 mm, packed with butyl silane chemically bonded to porous silica (5 µm),
- mobile phase: a mixture of 50 volumes of buffer solution prepared by dissolve 6.80 g of *monobasic potassium phosphate* with 900 ml of *water* and add 1 ml of *triethylamine,* adjusted to pH 6.0 with *orthophosphoric acid,* and dilute to 1000 ml with *water,* and 50 volumes of *acetonitrile,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 10 µl.

Inject the reference solutions. The test is not valid unless the column efficiency is not less than 1000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{25}H_{29}I_2NO_3$.HCl.

Chlorpheniramine Maleate. Page 1857

Identification.

Change **to**: In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (d).

Related substances

Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Solution A. Dissolve 5.44 g of *potassium dihydrogen phosphate* in 1000.0 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid*.

Solvent mixture. 95 volumes of solution A and 5 volumes of *acetonitrile*.

Test solution. Dissolve 50 mg of the substances under examination in the solvent mixture, with the aid of ultrasound for 1 minute and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.014 per cent w/v solution *chlorpheniramine Maleate IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 10.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.5 per cent w/v of *chlorpheniramine Maleate IPRS* and 0.002 per cent w/v, each of, *pheniramine Maleate IPRS*, *chlorpheniramine related compound B IPRS* and *chlorpheniramine related compound C IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (d). A 0.05 per cent w/v solution of *ciprofloxacin hydrochloride IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm),
- mobile phase: A. Solution A,
  B. *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
1	95	5
20	70	30
30	70	30
31	95	5
40	95	5

Name	Relative retention time	Correction Factor
Maleic acid[1]	0.18	--
Diamine analog[2]	0.37	1.37
Chlorpheniramine related compound B[3]	0.49	1.30
Pheniramine[4]	0.57	--
Chlorpheniramine related compound C[5]	0.97	--
Chlorpheniramine	1.0	--
Chlorpheniramine nitrile[6]	1.19	--

[1]salt counter ion is included in the table for identification purpose only,
[2]2-(4-Chlorophenyl)-4-(dimethylamino)-2-[2-(dimethylamino)ethyl]butanenitrile,
[3]Di(pyridine-2-yl)amine,
[4]Used only to establish the system suitability,
[5]3-(4-Chlorophenyl)-*N*-methyl-3-(pyridin-2-yl)propan-1-amine,
[6]2-(4-Chlorophenyl)-4-(dimethylamino)-2-(pyridin-2-yl)butanenitrile.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to chlorpheniramine related compound C and chlorpheniramine is not less than 1.5 and between the peaks due to Chlorpheniramine related compound B and chlorpheniramine is not less than 2.0 in the chromatogram obtained with reference solution (c), the relative standard deviation for replicate injections is not more than 5.0 per cent for chlorpheniramine in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 for chlorpheniramine peak in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to diamine analog is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). The area of any peak corresponding to, chlorpheniramine related compound B, chlorpheniramine related compound C and chlorpheniramine nitrile, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent). The area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak due to maleic acid with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Assay

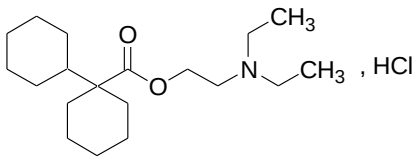
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14), as described under related substances with the following modifications.

Inject reference solution (c) and (d). The test is not valid unless the resolution between the peaks due to chlorpheniramine related compound C and chlorpheniramine is not less than 1.5 and chlorpheniramine related compound B and pheniramine is not less than 2.0 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (d).

Inject reference solution (d) and the test solution.

Calculate the content of $C_{16}H_{19}ClN_2,C_4H_4O_4$.

Dicyclomine Hydrochloride.Page 2091
Change **to:** **Dicyclomine Hydrochloride**



$C_{19}H_{35}NO_2$,HCl Mol.Wt. 346.0

Dicyclomine Hydrochloride is [Bicyclohexyl]-1-carboxylic acid, 2-(diethylamino) ethyl ester, hydrochloride.

Dicyclomine Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{19}H_{35}NO_2$,HCl calculated on the dried basis.

Category. Antispasmodic.

Description. A white or almost white, crystalline powder

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6).Compare the spectrum with that obtained with *dicyclomine hydrochloride IPRS* or with the reference spectrum of dicyclomine hydrochloride.

B. It gives reaction of chlorides (2.3.1).

C. In the Assay, the principle peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

pH (2.4.24). 5.0 to 5.5, determined in 1 per cent w/v solution in *water.*

Limit of Dicyclomine Related Compound A. Determine by liquid chromatography (2.4.14).

*Solvent mixture.*70 volumes of *acetonitrile* and 30 volumes of *water.*

Test solution. Dissolve 0.1 g of the substance under examination in the 20.0 ml solvent mixture with the aid of ultrasound, dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.003 per cent w/v solution of *dicyclomine hydrochloride related compound A IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). Dilute 5.0 ml reference solution (a) to 10.0 ml with the solvent mixture

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm packed with octylsilane bonded to porous silica (3.5µm),
- mobile phase: a mixture of 55 volumes of *acetonitrile* and 45 volumes of a buffer solution prepared by dissolving 2.72 g of *potassium dihydrogen orthophosphate* in 900 ml of *water*, adjusted to pH 7.5 with 10 per cent *sodium hydroxide* and dilute to 1000 ml with *water.*
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 100 µl

Inject reference solution (a) and (b) The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a), and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. The area of any peak corresponding to the area of any other secondary is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of areas of all the secondary peaks is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent)

Related substances. Determine by liquid chromatography (2.4.14).

NOTE--Use freshly prepared solutions.

*Solvent mixture.*70 volumes of *acetonitrile* and 30 volumes of *water.*

Test solution. Dissolve 40 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.04 per cent w/v solution of *dicyclomine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). Dilute 5.0 ml reference solution (b) to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm packed with octylsilane bonded to porous silica (3.5µm),
- mobile phase: a mixture of 70 volumes of *acetonitrile* and 30 volumes of a buffer solution prepared by dissolving 2.72 g of *potassium dihydrogen orthophosphate* in 900 ml of *water*, adjusted to pH 7.5 with 10 per cent *sodium hydroxide* and dilute to 1000 ml with *water.*
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 50 µl

Name	Relative retention time	Correction factor
Dicyclomine -1-ene [1]	0.8	0.34
Dicyclomine	1.0	--

[1]2-(Diethylamino) ethyl [1,1′-bi(cyclohexan)]-1′-ene-1-carboxylate,

Inject reference solution (a), (b) and (c).The test is not valid unless the resolution between the peaks due to *dicylomine* and *dicylomine-1-ene* is not less than 2.0 in the chromatogram obtained with reference solution (a), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (b) and the test solution. The area of any peak corresponding to dicyclomine-1-ene is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

The sum of areas of all the secondary peaks (Limit of Dicyclomine Related Compound A and Related substances) is not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent).

Heavy metals (2.3.13). 1.0 g complies with limit test for heavy metals, Method B (20 ppm).

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g by drying in an oven at 105° for 4 hours.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

NOTE--Use freshly prepared solutions

Inject reference solution (a).The the tailing factor is not more than 1.5 for dicyclomine peak and the relative standard deviation for replicate injections is not more than 0.73 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and test solution.

Calculate the content of $C_{19}H_{35}NO_2$,HCl.

Storage. Store protected from moisture.

Dicyclomine Injection. Page 2092
Change **to:** **Dicyclomine Injection**

Dicyclomine Hydrochloride Injection; Dicycloverine Hydrochloride Injection

Dicyclomine Injection is a sterile, isotonic solution of Dicyclomine Hydrochloride in Water for Injections.

Dicyclomine Injection contains not less than 93.0 per cent and not more than 107.0 per cent of the stated amount of dicyclomine hydrochloride, $C_{19}H_{35}NO_2$,HCl.

Usual strength. 10 mg per ml.

Identification

A. To a volume containing 0.1 g of Dicyclomine Hydrochloride add 10 ml of *water* and 1 ml of *hydrochloric acid,* shake with 30 ml of *ether* and allow to separate. Extract the aqueous layer with 30 ml of *chloroform,* wash the extract with two quantities, each of 20 ml, of *water* and 1ml of 10 per cent w/v sodium hydroxide. Filter the chloroform solution through *anhydrous sodium sulphate.* Add 3 mL of a freshly prepared 5 per cent w/v solution of *acetyl chloride* in *anhydrous methanol* (prepared by adding *acetyl chloride* dropwise to *anhydrous methanol* with stirring). Evaporate under reduced pressure at room temperature until the residue has been thoroughly dried. Use the residue so obtained evaporate the filtrate to dryness,

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *dicyclomine hydrochloride IPRS* treated in the same manner or with the reference spectrum of dicyclomine hydrochloride.

B. In the Assay the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Bacterial endotoxins (2.2.3). Not more than 17.2 Endotoxin Unit per mg of Dicyclomine Hydrochloride.

Other tests. Comply with the tests stated under Parental Preparations (Injections).

Limit of Dicyclomine Related Compound A. Determine by liquid chromatography (2.4.14).

*Solvent mixture.*70 volumes of *acetonitrile* and 30 volumes of *water*.

Test solution. Prepare a composite sample and transfer a volume containing about 20 mg of Dicyclomine Hydrochloride to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.004 per cent w/v solution of *dicyclomine hydrochloride related compound A IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). Dilute 5.0 ml reference solution (a) to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm packed with octylsilane bonded to porous silica (3.5µm),
- mobile phase: a mixture of 55 volumes of *acetonitrile* and 45 volumes of a buffer solution prepared by dissolving 2.72 g of *potassium dihydrogen orthophosphate* in 900 ml of *water*, adjusted to pH 3.5 with *orthophosphoric acid* and dilute to 1000 ml with *water*.
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 100 µl

Inject reference solution (a) and (b) The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a), and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. The area of any peak corresponding to dicyclomine hydrochloride related compound A is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Other tests. Comply with the tests stated under Parental Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

NOTE--Use freshly prepared solutions

*Solvent mixture.*70 volumes of *acetonitrile* and 30 volumes of *water.*

Test solution. Prepare a composite sample and transfer a volume containing about 20 mg of Dicyclomine Hydrochloride to 50.0 ml with the solvent mixture.

Reference solution . A 0.04 per cent w/v solution of *dicyclomine hydrochloride IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm packed with octylsilane bonded to porous silica (3.5µm),
- mobile phase: a mixture of 70 volumes of *acetonitrile* and 30 volumes of a buffer solution prepared by dissolving 2.72 g of *potassium dihydrogen orthophosphate* in 900 ml of *water*, adjusted to pH 7.5 with 10 per cent *sodium hydroxide* and dilute to 1000 ml with *water.*
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 50 µl

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{19}H_{35}NO_2$,HCl in the injection.

Storage. Store protected from light, in single dose or multipledose containers.

Fluconazole. Page 2364

Changed **to: Identification** B.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution.

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.3 g of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution. A solution containing 0.01 per cent w/v, each of, *fluconazole IPRS, fluconazole impurity A IPRS, fluconazole impurity B IPRS* and *fluconazole impurity C IPRS,* in *acetonitrile.* Dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- column temperature. 40°,
- mobile phase: 80 volumes of *water* and 20 volumes of *acetonitrile,*
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 260 nm,
- injection volume: 20 µl.

Name	Relative retention time
Fluconazole impurity A[1]	0.5
Specified impurity[2]	0.6
Fluconazole impurity B[3]	0.81
Fluconazole impurity C[4]	0.86
Fluconazole	1.0

[1]2-[2-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[2] unknown structure,
[3]2-(4-Fluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[4]1,1′-(1,3-Phenylene)di(1H-1,2,4-triazole).

Inject the reference solutions. The test is not valid unless the resolution between the peaks due to fluconazole impurity B and fluconazole impurity C is not less than 1.5 and the relative standard deviation for each peaks is not more than 5.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to fluconazole impurity A and fluconazole impurity C, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (0.2 per cent), the area of any peak corresponding to fluconazole impurity B is not more than 0.3 times the area of the corresponding peak in the chromatogram obtained with reference solution (0.1 per cent), the area of any peak corresponding to specified impurity at relative retention time about 0.6 is not more than 3.0 times the area of the peak in the chromatogram obtained with the reference solution (1.0 per cent). The area of any other secondary peak is not more than 0.3 times the area of the peak in the chromatogram obtained with the reference solution (0.1 per cent), the sum of the areas of all the other secondary peaks is not more than the area of the peak in the chromatogram obtained with the reference solution (0.3 per cent), and the sum of the areas of all the secondary peaks is not more than 4.5 times the area of the peak in the chromatogram obtained with the reference solution (1.5 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution. A 0.05 per cent w/v solution of *fluconazole IPRS* in the mobile phase.

Use the chromatographic system as described under Related substances.

Inject the reference solutions. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{12}F_2N_6O$.

Fluconazole Tablets. Page 2368

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the powdered tablets containing 0.3 mg of Fluconazole mobile phase A, with the aid of utrasound for 30 minutes with occasional swirling and dilute to 100.0 ml with mobile phase A, filter.

Reference solution (a). A 0.001 per cent w/v solution of *fluconazole IPRS* in mobile phase A.

Reference solution (b). A solution containing 0.001 per cent w/v of *fluconazole IPRS* and 0.0006 per cent w/v, each of, *fluconazole impurity A IPRS, fluconazole impurity B IPRS* and *fluconazole impurity C IPRS,* in mobile phase A.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- mobile phase: A. a mixture 85 volumes of *water* and 15 volumes of *acetonitrile,*
  B. *acetonitrile,*
- flow rate: 1 ml per minute,
-a gradient programme using the conditions given below,
- spectrophotometer set at 260 nm,
- injection volume: 25 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
16	100	0
50	90	10
55	100	0
65	100	0

Name	Relative retention time
Fluconazole impurity A[1*]	0.43
Fluconazole impurity B[2*]	0.72
Fluconazole impurity C[3*]	0.83
Fluconazole	1.0

*Process impurity included for identification only to be included in total degradation product.
[1]2-[2-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[2]2-(4-Fluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[3]1,1′-(1,3-Phenylene)di(1H-1,2,4-triazole).

Inject reference solution (b) to identify the peaks due to fluconazole impurity A, B and C.

Inject reference solutions (a). The test is not valid unless the relative standard deviation is not more than 5.0 per cent.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.3 times that of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Frusemide. Page 2433

Identification C

Changed **to:** C. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution.

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Protect Frusemide solutions from exposure to light.

Solvent mixture. 22 volumes of *glacial acetic acid* with a mixture of equal volumes of *acetonitrile* and *water* to 1000 ml.

Test solution. Dissolve 50 mg of the substance under examination in 50.0 ml of solvent mixture.

Reference solution (a). A solution containing 0.005 per cent w/v, each of, *frusemide impurity A IPRS* and *frusemide impurity B IPRS,* in solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.002 per cent w/v of *frusemide IPRS* and 0.0012 per cent w/v of *frusemide impurity A IPRS* in solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Spherisorb ODS),
- mobile phase: 30 volumes of *tetrahydrofuran,* 1 volume of *glacial acetic acid* and 70 volumes of *water,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm and 272 nm, *[NOTE—The 2,4-dichloro-5-sulfamoylbenzoic acid impurity does not respond at 272 nm, and the 2,4-bis(furfurylamino)-5-sulfamoylbenzoic acid impurity has a very intense absorbance at 254 nm. The response for frusemide is at 254 nm.]*
- injection volume: 20 µl.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to frusemide and frusemide impurity A is not less than 2.5 and the relative standard deviation for each peak is not more than 2.0 per cent.

Inject reference solution (a) and the test solution at 254 nm. Run the chromatogram 2.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the sum of areas of all the secondary peaks eluting before the frusemide is not more than the area of the frusemide impurity B in the chromatogram obtained with reference solution (a) (0.5 per cent).

Inject reference solution (a) and the test solution at 272 nm. Run the chromatogram 2.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the sum of areas of all the secondary peaks eluting after the frusemide is not more than the area of the frusemide impurity A in the chromatogram obtained with reference solution (a) (0.5 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

NOTE- Protect Frusemide solutions from exposure to light.

Test solution. Dissolve 20 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution. A 0.02 per cent w/v solution of *frusemide IPRS* in the solvent mixture.

Use the chromatographic system as described under Related substances using spectrophotometer set at 272 nm.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to frusemide and frusemide impurity A is not less than 2.5 and the relative standard deviation for each peak is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{12}H_{11}ClN_2O_5S$.

Frusemide Injection. Page 2434

Related substances. Change **to:**
Limit of Frusemide Impurity B. Determine by liquid chromatography (2.4.14).

NOTE- Protect Frusemide solutions from exposure to light.

Solvent mixture. 22 volumes of *glacial acetic acid* with a mixture of equal volumes of *acetonitrile* and *water* to 1000 ml.

Test solution. Transfer a measured volume of the injection containing equivalent to about 10 mg of Frusemide, to a 10-m1 volumetric flask, dilute to volume with the solvent mixture and mix.

Reference solution (a). A 0.001 per cent w/v solution of *frusemide impurity B IPRS* in solvent mixture.

Reference solution (b). A solution containing 0.002 per cent w/v of *frusemide IPRS* and 0.0012 per cent w/v of *frusemide impurity A IPRS* in solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Spherisorb ODS),
- mobile phase: 30 volumes of *tetrahydrofuran,* 1 volume of *glacial acetic acid* and 70 volumes of *water,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm and 272 nm, *[NOTE—The 2,4-dichloro-5-sulfamoylbenzoic acid impurity does not respond at 272 nm, and the 2,4-bis(furfurylamino)-5-sulfamoylbenzoic acid impurity has a very intense absorbance at 254 nm. The response for frusemide is at 254 nm.]*
- injection volume: 20 µl.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to frusemide and frusemide impurity A is not less than 2.5 and the relative standard deviation for each peak is not more than 2.0 per cent [NOTE—The response for frusemide is at 254 nm].

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the response at 254 nm obtained for any peak at a retention time corresponding to that of *frusemide impurity B IPRS* is not greater than the response obtained for the peak in the chromatogram of the reference solution (a) corresponding to not more than 1.0 per cent of frusemide impurity B.

For veterinary use.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the response at 254 nm obtained for any peak at a retention time corresponding to that of *frusemide impurity B IPRS* is not greater than 2.5 times the response obtained for the peak in the chromatogram of the reference solution (a) corresponding to not more than 2.5 per cent of frusemide impurity B.

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

NOTE- Protect Frusemide solutions from exposure to light.

Test solution. Transfer a measured volume of the injection containing equivalent to about 10 mg of Frusemide, to a 10-m1 volumetric flask, dilute to volume with the solvent mixture and mix.

Reference solution. A 0.1 per cent w/v solution of *frusemide IPRS* in the solvent mixture.

Use the chromatographic system as described under Related substances using spectrophotometer set at 254 nm.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to frusemide and frusemide impurity A is not less than 2.5 and the relative standard deviation for each peak is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{12}H_{11}ClN_2O_5S$ in the injection.

Frusemide Tablets. Page 2434

Related substances. Change **to:**
Limit of Frusemide Impurity B. Determine by liquid chromatography (2.4.14).

NOTE- Protect Frusemide solutions from exposure to light.

Solvent mixture. 22 volumes of *glacial acetic acid* with a mixture of equal volumes of *acetonitrile* and *water* to 1000 ml.

Test solution. Disperse a quantity of powdered tablets containing equivalent to about 10 mg of Frusemide, to a 10-m1 volumetric flask, dilute to volume with the solvent mixture and mix.

Reference solution (a). A 0.0008 per cent w/v solution of *frusemide impurity B IPRS* in solvent mixture.

Reference solution (b). A solution containing 0.002 per cent w/v of *frusemide IPRS* and 0.0012 per cent w/v of *frusemide impurity A IPRS* in solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Spherisorb ODS),
- mobile phase: 30 volumes of *tetrahydrofuran*, 1 volume of *glacial acetic acid* and 70 volumes of *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm and 272 nm, *[NOTE—The 2,4-dichloro-5-sulfamoylbenzoic acid impurity does not respond at 272 nm, and the 2,4-bis(furfurylamino)-5-sulfamoylbenzoic acid impurity has a very intense absorbance at 254 nm. The response for frusemide is at 254 nm].*
- injection volume: 20 µl.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to frusemide and frusemide impurity A is not less than 2.5 and the relative standard deviation for each peak is not more than 2.0 per cent [NOTE—The response for frusemide is at 254 nm].

Inject reference solution (a) and the test solution at 254 nm. In the chromatogram obtained with the test solution, the response obtained for any peak at a retention time corresponding to that of *frusemide impurity B IPRS* is not greater than the response obtained for the peak in the chromatogram of the reference solution (a) corresponding to not more than 0.8 per cent of frusemide impurity B.

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

NOTE- Protect Frusemide solutions from exposure to light.

Test solution. Weigh and powder 20 tablets. Weigh a quantity of the powder containing equivalent to about 50 mg of Frusemide, to a 50-ml volumetric flask, add 30 ml solvent mixture and sonicate for 10 minutes, dilute to volume with the solvent mixture and mix.

Reference solution. A 0.1 per cent w/v solution of *frusemide IPRS* in the solvent mixture.

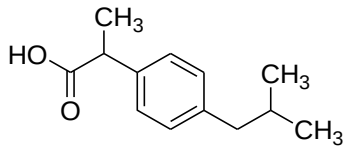
Use the chromatographic system as described under Related substances using spectrophotometer set at 254 nm.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to frusemide and frusemide impurity A is not less than 2.5 and the relative standard deviation for each peak is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{12}H_{11}ClN_2O_5S$ in the tablets.

Ibuprofen. Page 2571
Change **to**: **Ibuprofen**



$C_{13}H_{18}O_2$ Mol. Wt. 206.3

Ibuprofen is (2*RS*)-2-[4-(2-methylpropyl)phenyl]propanoic acid.

Ibuprofen contains not less than 98.5 per cent and not more than 101.0 per cent of $C_{I3}H_{18}O_2$, calculated on the dried basis.

Category. Anti-inflammatory; analgesic.

Description. A white or almost white, crystalline powder orcolourless crystals.

Identification

Test A may be omitted if tests B and C are carried out. Test B may be omitted if tests A and C are carried out.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ibuprofen IPRS* or with the reference spectrum of ibuprofen.

B. When examined in the range 230 nm to 360 nm (2.4.7), a0.05 per cent w/v solution in *0.1 M sodium hydroxide* shows absorption maxima at about 264 nm and 272 nm, and a shoulder at about 258 nm. The ratio of the absorbance at about 264 nm to that at the shoulder at about 258 nm is 1.20 to 1.30. The ratio of the absorbance at the maximum at about 272 nm to that at the shoulder at about 258 nm is 1.00 to 1.10.

C. In the Assay, the retention time of the principal peak in the chromatogram obtained with the test solution, corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Appearance of solution. A10.0 per cent w/v solution in *methanol* is clear (2.4.1), and colourless (2.4.1).

Optical rotation (2.4.22). +0.05° to -0.05°, determined in a2.5 per cent w/v solution in *methanol.*

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in 2 ml of *acetonitrile* and dilute to 10.0 ml with mobile phase A.

Reference solution (a). A 1.0 per cent w/v solution of *ibuprofen IPRS* in *acetonitrile*.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 100.0 ml with mobile phase A. Dilute 1.0 ml of the solution to 10.0 ml with mobile phase A.

Reference solution (c). Mix 2.0 ml of reference solution (a) and 1.0 ml of 0.006 per cent w/v solution of *ibuprofen impurity B IPRS ((2RS)-2-(4-butylphenyl) propanoic acid)* in *acetonitrile* and dilute to 10.0 ml with mobile phase A.

Reference solution (d). Mix 2.0 ml of reference solution (a) and 1.0 ml of 0.02 per cent w/v solution, each of, *ibuprofen impurity A IPRS, ibuprofen impurity J IPRS* and *ibuprofen impurity N IPRS* in *acetonitrile* and dilute to 10.0 ml with mobile phase A.

Chromatographic system

- a stainless steel column 15 cm × 4.6 mm, packed with end-capped octadecylsilane amorphous organosilica polymer (5 µm)(Such as XTerra MS C18),
- mobile phase: A. a mixture of 600 volumes of *water*, 340 volumes of *acetonitrile* and 0.5 volume of *orthophosphoric acid* and dilute to 1000 volumes with *water*,
B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 2 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 20µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
25	100	0
55	15	85
70	15	85
71	100	0
75	100	0

Name	Relative retention time
Ibuprofen impurity J[1]	0.2
Ibuprofen impurity N[2]	0.3
Ibuprofen impurity A[3]	0.9
Ibuprofen (retention time about 21 minutes)	1.0
Ibuprofen impurity B[4]	1.1

[1] (2RS)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid,
[2] (2RS)-2-(4-ethylphenyl)propanoic acid,
[3](2RS)-2-[3-(2-methylpropyl)phenyl]propanoic acid,
[4] (2RS)-2-(4-butylphenyl)propanoic acid,

Inject reference solution (c). The test is not valid unless the peak-to-valley ratio is not less than 1.5, where Hp is the height above the baseline of the peak due to ibuprofen impurity B and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen. If necessary, adjust the concentration of*acetonitrile* in the mobile phase to obtain the required resolution.

Inject reference solution (d) to identify the peaks corresponds to ibuprofen impurity A, J and N.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to, each of, ibuprofen impurity A, J and N is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent) and the sum of areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent). Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Impurity F. Not more than 0.1 per cent

Determine by gas chromatography (2.4.13).

Methylating solution. Dilute 1 ml *of N,N-dimethylformarnide dimethylacetal* and l ml *of pyridine* to 10 ml with *ethyl acetate.*

Test solution. Weigh about 50.0 mg of the substance under examination into a sealable vial, dissolve in 1.0 ml of *ethylacetate*, add 1 ml of the methylating solution, seal and heat at100° in a block heater for 20 minutes, cool. Remove the reagents under a stream of nitrogen at room temperature. Dissolve the residue in 5 ml of *ethyl acetate.*

Reference solution (a). Dissolve 0.5 mg of *ibuprofen impurity F IPRS*(3-[4-(2-methylpropyl)phenyl]propanoic acid)in *ethyl acetate* and dilute to 10.0 ml with *ethyl acetate.*

Reference solution (b). Weigh about 50.0 mg of *ibuprofen RS* into a sealable vial, dissolve in 1.0 ml of reference solution (a.), add 1 ml of the methylating solution, seal and heat at 100° in a block heater for 20 minutes. Allow to cool. Remove the reagents under a stream of nitrogen at room temperature. Dissolve the residue in 5 ml of *ethyl acetate.*

Chromatographic system
- a fused silica capillary column 25 m x 0.53 mm, coated with macrogol 20000 (film thickness 2 µm),
- temperature: column 150°,
- injector port: 200° and detector port at 250°,
- flame ionization detector,
- flow rate: 5.0 ml per minute using nitrogen as the carriergas.

The relative retention time with reference to ibuprofen (retention time about 17 minutes) for ibuprofen impurity F is about 1.5.

Inject 1 µl of reference solution (b) and the test solution. Runthe chromatogram twice the retention time of the principalpeak.

Calculate the content of ibuprofen impurity F.

Heavy metals (2.3.13). 2.0 g complies with the limit test for heavy metals, Method B (10 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying under vacuum.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.1 g of the substance under examination in50 ml of the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Reference solution. A 0.01 per cent w/v solution of *ibuprofen IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (10 µm) (Such as Nucleosil C18),
- mobile phase: a mixture of 75 volumes of *methanol*, 24.7 volumes of *water* and 0.3 volume of *orthophosphoric acid*,
- flow rate: 1.5 ml per minute,
- spectrophotometer: set at 264 nm,
- injection volume: 20µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{18}0_2$.

Storage. Store protected from moisture.

Solubility. Freely soluble in *acetone*, in *methanol* and in *methylene chloride*; practically insoluble in *water*. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Ibuprofen Oral Suspension

Ibuprofen Oral Suspension contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Ibuprofen, $C_{13}H_{18}O_2$.

Usual strengths. 50 mg per 5 ml; 100 mg per 5 ml.

Identification

Shake a quantity of the suspension containing 0.5 g of Ibuprofen with 25 ml of *dichloromethane* and 15 ml *water*. Allow to stand until the layers have separated and discard the upper layer. Shake the lower layer with 5 ml of *water* and discard the upper layer. Evaporate the lower layer to dryness, add 20 ml of *water* to the residue and filter.Wash the residue with 20 ml of *dichloromethane* and evaporate to dryness. The residue complies with the following test,

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ibuprofen IPRS* or with the reference spectrum of ibuprofen.

Tests

pH (2.4.24). 3.6 to 4.6.

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium.900 mlof *phosphate buffer pH 7.2*,
Speed and time. 50 rpm and 30 minutes.

Note- Shake the oral suspension for 30 seconds and place a volume of the oral suspension containing 0.2 g ofIbuprofen in to each dissolution vessel.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Dilute the filtrate, if necessary, with the dissolution medium.

Reference solution (a). A 0.0022 per cent w/v solution of *ibuprofen IPRS* in the dissolution medium.

Reference solution (b). A solution containing 0.03 per cent w/v, each of, *benzophenone* and *ibuprofen IPRS*in the dissolution medium.

Chromatographic system
- a stainless steel column 15 cm × 4.6mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase:a mixture of 63 volume of *0.01 M orthophosphoric acid* and 37 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 220nm,
- injection volume: 10 µl.

Inject reference solution (b). The test is not valid unless theresolution between the peaks due to benzophenone and ibuprofen is not less than 1.5.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{13}H_{18}O_2$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_{13}H_{18}O_2$.

Related substances.Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of oral suspension containing 0.2 g of Ibuprofen in 20 ml of *acetonitrile* with the aid of ultrasound and dilute to 100.0 ml with mobile phase A.

*Reference solution (a).*A 0.0002 per cent w/v solution of *ibuprofen IPRS*in the mobile phase A.

Reference solution (b). Dissolve 20 mg of *ibuprofen IPRS* in 2.0 ml of *acetonitrile,* add 1 ml of a 0.006 per cent w/v solution of *ibuprofen impurity B IPRS* in *acetonitrile* and dilute to 10.0 ml with mobile phase A.

*Reference solution (c).*A solution containing 0.0015 per cent w/v, each of, *ibuprofen impurity A IPRS, ibuprofen impurity J IPRS* and *ibuprofen impurity N IPRS* in *acetonitrile.* Dilute 1.0 ml of the solution to 10.0 ml with mobile phase A.

Reference solution (d). A 0.0006 per cent w/v solution of *ibuprofen impurity E IPRS* (4-isobutylacetophenone) in mobile phase A.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with end-capped octadecylsilane amorphous organosilica polymer (5 µm), (Such as XTerra MS C18),
- mobile phase: A. a mixture of 34 volumes of *acetonitrile*, 66 volumes of*water* and 0.05 volume of *orthophosphoric acid*,

B. a mixture of 10 volumes of *water*,90 volumes of *acetonitrile* and 0.05 volume of *orthophosphoric acid*,

- a gradient programme using the conditions given below,
- flow rate: 2 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
25	100	0
55	0	100
70	0	100
71	100	0
85	100	0

Name	Relative retention time
Ibuprofen impurity J[1]	0.2
Ibuprofen impurity N[2]	0.3
Ibuprofen impurity A[3]	0.9
Ibuprofen (Retention time: about 26 minutes)	1.0
Ibuprofen impurity B[4]	1.08
Ibuprofen impurity E[5]	1.11

[1](2RS)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid,
[2](2RS)-2-(4-ethylphenyl)propanoic acid,
[3](2RS)-2-[3-(2-methylpropyl)phenyl]propanoic acid,
[4](2RS)-2-(4-butylphenyl)propanoic acid,
[5]4-isobutylacetophenone

Inject reference solution (c) and (d) to identify the peaks due to ibuprofen impurity A, ibuprofen impurity J, ibuprofen impurity N and ibuprofen impurity E, respectively.

Inject reference solution (b). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is not less than 5.0, where Hp is the height above the baseline of the peak due to ibuprofen and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen impurity B.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to ibuprofen impurity E is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any peak corresponding to ibuprofen impurity A, ibuprofen impurity J andibuprofen impurity N, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of any secondary peaks is not more than 7 times of the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Other tests. Comply with the tests stated under Oral Liquids.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of oral suspension containing 0.1 g of Ibuprofen in 40 ml of *acetonitrile* and add 10 ml of *0.01 M orthophosphoric acid*,shake vigorously and dilute to 100.0 ml with *0.01 M orthophosphoric acid*, filter.

*Reference solution.*A 0.1 per cent w/v solution of *ibuprofen IPRS* in the mobile phase.

Chromatographic system

- a stainless steel column 30 cm x 3.9 mm, packed with end-capped octadecylsilane bonded to porous silica (10 µm), (Such as µBondapak C18),
- mobile phase: a mixture of 40 volumes of *acetonitrile* and 60 volumes of *0.01 M orthophosphoric acid*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 10 µl.

Inject the reference solution and the test solution.

Determine the weight per ml of the oral suspension (2.4.29) and calculate the content of $C_{13}H_{18}O_2$ in the suspension.

Storage. Store protected from light, at a temperature not exceeding 30°.

Ibuprofen Tablets. Page 2575
Change **to**: **Ibuprofen Tablets**

Ibuprofen Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of ibuprofen, $C_{13}H_{18}O_2$. The tablets are coated.

Usual strengths. 200 mg; 400 mg; 600 mg.

Identification
A. Extract a quantity of the powdered tablets containing 0.5 g of Ibuprofen with 20 ml of *acetone*, filter and evaporate the filtrate to dryness in a current of air without heating. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ibuprofen IPRS* or with the reference spectrum of ibuprofen.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with the test solution, corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 900 ml of *phosphate buffer pH 7.2*,
Speed and time. 50 rpm and 45 minutes.

Determine by liquid chromatography (2.4.14),

Test solution. Use the filtrate, dilute, if necessary, with the dissolution medium to obtain a solution containing 0.02 per cent w/v of ibuprofen.

Reference solution. A 0.02 per cent w/v solution *of ibuprofen IPRS* in the dissolution medium**.**

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous Silica(10 µm) (Such as Nucleosil C18),
- mobile phase: a mixture of 75 volumes of *methanol*, 24.7 volumes of *water* and 0.3 volume of *orthophosphoric acid*,
- flow rate: 1.5 ml per minute,
- spectrophotometer: set at 264 nm,
- injection volume: 20µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{18}O_2$ in the medium.

Q. Not less than 75.0 per cent of the stated amount of $C_{13}H_{18}O_2$.

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the powdered tabletscontaining 0.2g of ibuprofen in 20ml of *acetonitrile* with the aid of ultrasound, dilute to 100.0 ml with mobile phase Aand filter (Whatman GF/C is suitable).

Reference solution (a). A 1.0 per cent w/v solution of *ibuprofen IPRS* in *acetonitrile*.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 100.0 ml with mobile phase A. Dilute 1.0 ml of the solution to 10.0 ml with mobile phase A.

Reference solution (c). Mix 2.0 ml of reference solution (a) and 1.0 ml of 0.006 per cent w/v solution of *ibuprofen impurity B IPRS ((2RS)-2-(4-butylphenyl) propanoic acid)* in *acetonitrile* and dilute to 10.0 ml with mobile phase A.

*Reference solution (d).*A 0.0006% w/v solution of *ibuprofen impurity E IPRS* (4-isobutylacetophenone) in the mobile phase A.

Reference solution (e). Mix 2.0 ml of reference solution (a) and 1.0 ml of 0.02 per cent w/v solution, each of, *ibuprofen impurity A IPRS, ibuprofen impurity J IPRS* and *ibuprofen impurity N IPRS* in *acetonitrile* and dilute to 10.0 ml with mobile phase A.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with end-capped octadecylsilane amorphous organosilica polymer (5 µm), (Such as XTerra MS C18),
- mobile phase: A. mix 340 volumes of *acetonitrile,* 0.5 volume of *orthophosphoric acid* and dilute with *water* to produce 1000volumes,
  B. mix 100 volumes of *water*, 0.5 volume of *orthophosphoric acid* and dilute with *acetonitrile* to produce 1000volumes,
- a gradient programme using the conditions given below,
- flow rate: 2.0 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
25	100	0
55	0	100
70	0	100
71	100	0
85	100	0

Name	Relative retention time
Ibuprofen impurity J[1]	0.2
Ibuprofen impurity N[2]	0.3
Ibuprofen impurity A[3]	0.9
Ibuprofen impurity B[4]	1.08
Ibuprofen (retention time about 26 minutes)	1.0
Ibuprofen impurity E[5]	1.11

[1] (2RS)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid,
[2] (2RS)-2-(4-ethylphenyl)propanoic acid,
[3](2RS)-2-[3-(2-methylpropyl)phenyl]propanoic acid,
[4] (2RS)-2-(4-butylphenyl)propanoic acid,
[5]4-isobutylacetophenone,

Inject reference solution (c). The test is not valid unless the peak-to-valley ratio is not less than 5.0, where Hp is the height above the baseline of the peak due to ibuprofen impurity B and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

Inject reference solution (d) and (e). Use the chromatogram obtained with reference solution (d) to identify the peaks corresponds to ibuprofen impurity E and chromatogram obtained with reference solution (e) to identify the peaks corresponds to ibuprofen impurity A, J and N.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area any peak corresponding to ibuprofen impurity E is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent) and the area of any peak corresponding to ibuprofen impurity A, J or N, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 7 times the area of the principal peak in the

chromatogram obtained with reference solution (b) (0.7 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1g of ibuprofen in50 ml of the mobile phase and dilute to 100.0 ml with the mobile phase. Centrifuge and dilute 1.0 ml of the supernatant liquid to 10.0 ml with the mobile phase.

Reference solution. A 0.01 per cent w/v solution of *ibuprofen IPRS* in the mobile phase.

Use the chromatographic system as described under Dissolution.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{18}O_2$ in the tablets.

Storage. Store protected from moisture.

Ketoconazole. Page 2352

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Buffer solution : a 0.34 per cent w/v solution of *tetrabutyl ammonium sulfate* in *water*.

Test solution. Dissolve 0.1 g of the substance under examination in 10.0 ml of *methanol.*

Reference solution. Dissolve 2.5 mg each of *ketoconazole IPRS* and *terconazole IPRS* in 25 ml of *methanol.* Dilute 10.0 ml of the solution to 100.0 ml with the *methanol*.

Chromatographic system
- a stainless steel column 10 cm x 4.6 mm, packed with octadecylsilyl bonded to porous silica (3µm),
- mobile phase: A. a mixture of 95 volumes of a buffer solution and 5 volumes of *acetonitrile*,
  B. a mixture of 50 volumes of a buffer solution and 50 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 10 µl.

Time (min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
20	0	100
25	0	100
26	100	0
30	100	0

Inject reference solution. The test is not valid unless the resolution between the peaks due to ketoconazole and terconazole is not less than 2.0 and the Relative standard deviation for the replication peak is not less than 5.0 per cent.

Inject reference solution and the test solution. In the chromatogram obtained with the test solution the areas of all the secondary peaks is not more than the area of principal peak in the chromatogram obtained with with reference Solution (0.10 per cent) and the sum of the areas of all the secondary peaks is not more than 20 times the area of the peak in the chromatogram obtained with reference solution (b) (2.0 per cent). Ignore any peak with an area less than 0.5 times that of the principal peak in the chromatogram obtained with reference solution (0.05 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14). as described in the Related substances with the following modification.
Test solution. Dissolve 0.1 g of the substance under examination in 100.0 ml of *methanol.* Dilute 10.0 ml of the solution to 100.0 ml with the *methanol*.

Reference solution. A 0.01 per cent w/v solution of *ketoconazole IPRS* in the *methanol.*

Inject reference solution. The tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 0.73 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{26}H_{28}Cl_2N_4O_4$.

Linezolid. Page 2766

Identification B, line 3

Change **from** : reference solution (b)
to : reference solution (c)

Tests

Specific optical rotation. Delete the requirement.

Insert before **Related substance.**

Enantiomeric purity. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in *ethanol* with the aid of ultrasound and dilute to 100.0 ml with *ethanol*.

Reference solution. A solution containing 0.0025 per cent w/v, each of, *linezolid IPRS* and *linezolid R isomer IPRS*, in *ethanol*.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, Amylose tris-3,5-dimethylphenylcarbamate-coated, porous silica (5 µm) (Such as Chiral pak AD-H),
- mobile phase: a mixture of 65 volumes of *hexane*, 35 volumes of *ethanol* and 0.1 volume of *trifluoroacetic acid*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Name	Relative retention time
Linezolid R isomer[1]	0.84
Linezolid	1.0

[1]N-{[(R)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl}acetamide.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to linezolid and linezolid R isomer is not less than 1.5.

Inject the test solution. Run the chromatogram 2-8 times the retention time of the principal peak, the area of any peak corresponding to linezolid R isomer is not more than 0.3 per cent, calculated by area normalization.

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Buffer solution. A solution prepared by dissolving 1.4 g of *monobasic potassium phosphate* in 1000 ml of *water.*

Solvent mixture. 65 volumes of *water* and 35 volumes of *methanol.*

Test solution(a). Dissolve 80 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.
Test solution(b). Dilute 1.0 ml of test solution (a) to 10.0 ml with the solvent mixture.

Reference solution(a) A 0.008 per cent w/v solution of *linezolid IPRS* in the solvent mixture.

Reference solution(b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Reference solution(c). A solution containing 0.005 per cent w/v, each of, *linezolid IPRS* and *linezolid related compound D IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 7.5 cm x 4.6 mm, packed with Octadecylsilane bonded to porous silica (3 µm) (Such as Discovery HS C18),
- Sample temperature 15º
- mobile phase: A**.** a mixture of 80 volumes of the buffer solution, 15 volumes of *methanol* and 5 volumes of *acetronitrile,*

  B. a mixture of 50 volumes of the buffer solution and 50 volumes of *methanol,*

  flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl,

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
8	57	43
18	0	100
25	0	100
25.1	80	20
30	80	20

Name	Relative retention time
Linezolid N- oxide[1]	0.20
Linezolid related compound C[2]	0.31
Desfluoro linezolid[3]*(if present)	0.63
Linezolid	1.0
Linezolid related compound D[4]	1.4

*If possible from the manufacturing process,
[1](*S*)-4-{4-[5-(Acetamidomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}morpholine 4-oxide,
[2](*S*)-5-(Aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (linezolid amine),
[3](*S*)-*N*-{[3-(4-Morpholinophenyl)-2-oxooxazolidin-5-yl]methyl}acetamide,
[4](*R*)-[3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl]methyl methanesulfonate.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to linezolid and linezolid related compound D is not less than 3.0 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution (a). In the chromatogram obtained with the test solution (a), the area of any peak corresponding to linezolid N- oxide and desfluoro linezolid, each of is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent), the area of any peak corresponding to linezolid related compound C, is not more than twice the area of principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution(a) (0.10 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution(a) (0.05 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14). as described under Related substances with following modifications.

Inject reference solution (a) and (c) The test is not valid unless the resolution between the peaks due to linezolid and linezolid related compound D is not less than 3.0 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{16}H_{20}FN_3O_4$.

Comparision

Monograph Name	Test name	IP 2018	USP	BP 2022	Status
Linezolid	Related substance Test	No specified impurity used in Rs test	Linezolid related comp D used		Upgraded from USP
	Identification test	**A.** By IR **B.** By UV	**A.** By IR B. By Assay		Identification B upgraded as per usp
	Assay	By Hplc	By Hplc		Upgraded from USP
	Enantiomeric purity	NA	By Hplc		Upgraded from USP
Linezolid Tablets	Related substance Test	No specify imp used	Monograph not available	Monograph not available	No need to upgrade
	Identification test	By assay			
	Assay	By hplc			

Metronidazole Injection. Page 2924

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a suitable volume of the injection with the mobile phase to obtain a solution containing 0.05 per cent w/v of Metronidazole.

Reference solution (a). A solution containing 0.0075 per cent w/v each of *metronidazole IPRS* and *tinidazole related compound A IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (b). A solution containing 0.0001 per cent w/v of *metronidazole IPRS* and 0.0002 per cent w/v of *tinidazole related compound A IPRS* in the mobile phase.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 um),
- mobile phase: a mixture of 20 volumes of *methanol* and 80 volumes of *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 319 nm,
- injection volume: 30µl.

Name	Relative retention time	Correction factor
Tinidazole related compound A[1]	0.7	---
Metronidazole	1.0	---

[1] 2-Methyl-5-nitroimidazole.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to metronidazole and tinidazole related compound A is not less than 4.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to tinidazole related compound A, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent) and the sum of areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14). as described under Related substances with the following modifications.

Test solution. Dilute a suitable volume of the injection with mobile phase to obtain a solution containing 0.003 per cent w/v of Metronidazole.

Reference solution (a). A solution containing 0.003 per cent w/v of *metronidazole IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.0001 per cent w/v of *metronidazole IPRS* and 0.002 per cent w/v of *tinidazole related compound A IPRS* in the mobile phase.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to metronidazole and tinidazole related compound A is not less than 4.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a) .

Inject the reference solution (a) and the test solution.

Calculate the content of $C_6H_9N_3O_3$ in the injection.

Miconazole Nitrate. Page 2935

Identification. C

Change **to**:

C. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution (a).

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 70 volumes of *methanol* and 30 volumes of *water.*

Test solution. Dissolve 60 mg of the substance under examination in the solvent mixture with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture.

Reference solution. A solution containing 0.00012 per cent w/v, each of, *miconazole nitrate IPRS, econazole nitrate IPRS, miconazole related compound C IPRS , miconazole related compound F* and *miconazole related compound I IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 10 cm x 4.6 mm, packed with phenyl groups bonded to porous silica (2.6 um) (Such as Kinetex phenyl- Hexyl),
- column temperature: 40°,
- mobile phase: A. a mixture of 70 volumes of *water,* 30 volumes of *methanol* and 1 volume of *1M triethylammonium acetate*,
- B. a mixture of 75 volumes of *methanol*, 25 volumes of *acetronitrile* and 0.2 volume of *1M triethylammonium acetate*,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	70	30
5	70	30
10	44	56
27	44	56
30	25	75
35.1	25	75
36	70	30
40	70	30

Name	Relative retention time	correction factor
Deschlorbenzyl econazole[1]	0.22	---
Miconazole quarternary salt[2]	0.57	
Miconazole benzyl analog[3]	0.65	
Miconazole Related compound C[4]	0.74	
Miconazole Related compound I[5]	0.76	
Econazole nitrate	0.78	
Miconazole 2,6- isomer[6]	0.87	
Miconazole 2,5- isomer[7]	0.94	
Miconazole Related compound F[8]	0.96	

[1]1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol,
[2]2-(3-{2-[(2,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazol-3-ium-1-yl)-2-methylpropanoate,
[3] 1-[2-(Benzyloxy)-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,
[4]2-[(2,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethan-1-amine hydrochloride,
[5]1-{2-[(2-Chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole mononitrate,
[6]1-{2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole,
[7] 1-{2-[(2,5-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole,
[8]1-{2-[(3,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole.

Inject reference solution. The test is not valid unless the resolution between the peaks due to miconazole related compound C and miconazole related compound I is not less than 1.5, between the peaks due to miconazole related compound I and econazole is not less than 1.5 and between the peaks due to miconazole related compound F and miconazole is not less than 1.5 and the relative standard deviation for replicate injections is not more than 3.0 per cent for miconazole peak.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to miconazole related compound C, miconazole related compound F, miconazole related compound I and econazole nitrate, each of, is not more than 1.25 times the area of the corresponding peaks in the chromatogram obtained with the reference solution. (0.25 per cent), the area of any peak corresponding to deschlorbenzyl econazole, miconazole quarternary salt, miconazole benzyl analog, miconazole 2,6- isomer and miconazole 2,5- isomer, each of, is not more than 1.25 times the area of the principal peak in the chromatogram obtained with the reference solution (0.25 per cent), the area of any other secondary peak is not more than 0.5 times the area of principal peak in the chromatogram obtained with reference solution (0.10 per cent) and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14). as described under Related substances with the following modifications.

Test solution. Dissolve 100 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.01 per cent w/v solution of *miconazole nitrate IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.01 per cent w/v of *miconazole nitrate IPRS* and 0.0006 per cent w/v of *miconazole related compound F IPRS* in the solvent mixture.

The relative retention time with reference to miconazole, for miconazole related compound F is about 0.96.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to miconazole related compound F and miconazole is not less than 1.5 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{18}H_{14}Cl_4N_2O.HNO_3$.

Mometasone Furoate. Page 2624

Identification. C

Change **to:** C. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Prepare the solution immediately before use and protect from light.

Solvent mixture. 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *glacial acetic acid*.

Test solution (a). Dissolve 25.0 mg of the substance under examination in 15 ml of *acetonitrile* and dilute to 50.0 ml with the solvent mixture.

Test solution (b). Dilute 5.0 ml of test solution (a) to 25.0 ml with the solvent mixture.

Reference solution (a). Dissolve 25.0 mg of *mometasone furoate IPRS* in 15 ml of *acetonitrile* and dilute to 50.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 25.0 ml with the solvent mixture

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Further dilute 1.0 m1 of this solution to 10.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.5 per cent w/v of *momentasone furoate IPRS* and 0.005 per cent w/v each of, *momentasone furoate impurity J IPRS*, *momentasone furoate impurity C IPRS* in *acetonitrile*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Name	Relative retention time
Mometasone furoate impurity C[1]	0.9
Mometasone furoate (Retention time about 24 minutes)	1.0
Mometasone furoate impurity J[2]	1.5

[1] 21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,
[2] 9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Inject reference solution (c) to identify the peaks due to momentasone furoate impurity J and C.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to momentasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (b) and test solution (a). Run the chromatogram 3.5 times the retention time of the principal peak, the area of any peak corresponding to impurity J is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent). The area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peak is not more than 3 times the area of the principal peak in the chromatogram obtained with

reference solution (b) (0.3 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to:**

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with the following modification.

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{27}H_{30}Cl_2O_6$.

Mometasone Cream. Page 2626

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Prepare solutions immediately before use and protect from light.

Solvent mixture (a). 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *glacial acetic acid*,
Solvent mixture (b). 45 volumes of *acetonitrile* and 55 volumes of solvent mixture (a).

Test solution. Disperse a quantity of the cream containing about 10 mg of Mometasone Furoate in 45 ml of *acetonitrile* by heating on a water-bath at 60° with intermittent shaking for 60 minutes. Place in freezer for 30 minutes, shake with to 55.0 ml of solvent mixture (a). Centrifuge and filter.

Reference solution (a). A 0.1 per cent w/v solution of *momentasone furoate IPRS* in *acetonitrile.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with the solvent mixture (b).

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 200.0 ml with the solvent mixture (b).

Reference solution (d). A solution containing 0.001 per cent w/v of *momentasone furoate IPRS* and 0.0001 per cent w/v each of, *momentasone furoate impurity J IPRS*, *momentasone furoate impurity C IPRS* in *acetonitrile*. Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture (a).

Reference solution (e). Dilute 2.0 ml of reference solution (c) to 10.0 ml with solvent mixture (b).

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254nm,
- injection volume: 20 µl.

Name	Relative retention time
Mometasone furoate impurity C[1]	0.9
Mometasone furoate (Retention time about 25 minutes)	1.0
Mometasone furoate impurity J[2]	1.5

[1] 21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,
[2] 9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Inject reference solutions (d). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (c), (e) and the test solution. Run the chromatogram 2.5 times the retention time of the principal peak, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent) and the sum of the areas of all the secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent).

Assay. Change **to:**

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with the following modification.

Inject reference solutions (d). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (b) and the test solution.

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the cream.

Mometasone Aqueous Nasal Spray. Page 2626

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Prepare solutions immediately before use and protect from light.

Solvent mixture (a). 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *glacial acetic acid.*

Solvent mixture (b). 6 volumes of *acetonitrile* and 94 volumes of solvent mixture (a).

Test solution. Discharge the container a sufficient number of time to obtain 1 mg of Mometasone Furoate, add 3 ml of *acetonitrile* and 2 ml of solvent mixture (a). Mix with the aid of ultrasound and dilute to 10.0 ml with solvent mixture (a) and centrifuge.

Reference solution (a). A 0.1 per cent w/v of *momentasone furoate IPRS* in *acetonitrile.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with the solvent mixture (b).

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 20.0 ml with the solvent mixture (a).

Reference solution (d). A solution containing 0.01 per cent w/v of *momentasone furoate IPRS* and 0.0001 per cent w/v, each of, *momentasone furoate impurity J IPRS* and *momentasone furoate impurity C IPRS*, in *acetonitrile.*Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture (a).

Reference solution (e). Dilute 1.0 ml of reference solution (c) to 20.0 ml with solvent mixture (a).

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254nm,
- injection volume: 20 µl.

Name	Relative retention time
Mometasone furoate impurity C[1]	0.9
Mometasone furoate (Retention time about 24 minutes)	1.0
Mometasone furoate impurity J[2]	1.5

[1] 21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,
[2] 9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Inject reference solutions (d). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (c), (e) and the test solution. run the chromatogram 2.5 times the retention time of the principal peak, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent) and the sum of the areas of all the secondary peak is not more than 4.0 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent).

Assay. Change **to:**

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with the following modification.

Inject reference solutions (d). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (b) and the test solution.

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the nasal spray.

Mometasone Ointment. Page 2627

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Prepare solutions immediately before use and protect from light.

Solvent mixture (a). 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *glacial acetic acid*.

Solvent mixture (b). 45 volumes of *acetonitrile* and 55 volumes of solvent mixture (a).

Test solution. Disperse a quantity of the ointment containing about 10 mg of Mometasone Furoate in 25 ml of *acetonitrile* by heating on a water-bath at 80° and allow to cool. Add 20 ml of *acetonitrile* and 30 ml of solvent mixture (a), shake for 30 minutes and dilute to 100.0 ml with solvent mixture (a), centrifuge and filter.

Reference solution (a). A 0.1 per cent w/v solution of *momentasone furoate IPRS in acetonitrile.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with the solvent mixture (b).

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 200.0 ml with the solvent mixture (b).

Reference solution (d). A solution containing 0.001 per cent w/v of *momentasone furoate IPRS* and 0.0001 per cent w/v each of, *momentasone furoate impurity C IPRS, momentasone furoate impurity J IPRS* in *acetonitrile*. Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture (a).

Reference solution (e). Dilute 2.0 ml of reference solution (c) to 10.0 ml with the solvent mixture (b).

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254nm,
- injection volume: 20 µl.

Name	Relative retention time
Mometasone furoate impurity C[1]	0.9
Mometasone furoate (Retention time about 25 minutes)	1.0
Mometasone furoate impurity J[2]	1.5

[1] 21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,
[2] 9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Injection reference solution (d) to identify the peak due to mometasone furoate impurity C and J.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (c), (e) and the test solution. Run the chromatogram 2.5 times the retention time of the principal peak, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent) and the sum of the areas of all the secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent).

Assay. Change **to:**

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with the following modification.

Inject reference solutions (d). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (b) and the test solution.

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the ointment.

Phenylephrine Injection. Page 2911

Para 2

Change **to**: phenylepherine Injection contains not less than 90 per cent and not more than 115.0 per cent of the stated amount of phenylepherine hydrochloride, $C_9H_{13}NO_2$,HCI.

Identification. A

Change **to**: A.

A. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a suitable volume of injection with *water* to obtained 0.01 per cent w/v of Phenylephrine Hydrochloride.

Reference solution (a). A solution containing 0.002 per cent w/v of *phenylephrine hydrochloride IPRS* in *water*. Dilute 1.0 ml of the solution to 100.0 ml with *water*.

Reference solution (b). A solution containing 0.01 per cent w/v of *phenylephrine hydrochloride IPRS* and 0.0005 per cent w/v solution of *phenylephrine impurity F IPRS* in the *water*.

Reference solution (c). Dilute 5.0 ml of reference solution (a) to 10.0 ml with *water*.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with endcapped octadecylsilane bonded to porous silica (2.6 um) (Such as Kinetix XB-C-18),
- column temperature: 35°,
- mobile phase: A. a 0.1 per cent v/v of *orthophosphoric acid* in *water*,
  B. *acetonitrile,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 10µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	98	2
2.5	98	2
6	65	35
6.1	98	2
9	98	2

Name	Relative retention time	Correction factor
Phenylephrine	1.0	----
Phenylephrine related compound C[1]	1.2	0.36
Phenylephrine citrate adduct[2]	2.9	---

[1] 1(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one hydrochloride,
[2] 2-Hydroxy-2-(2-{[(*R*)-2-hydroxy-2-(3-hydroxyphenyl)ethyl](methyl)amino}-2-oxoethyl)succinic acid.

Inject reference solution (a) (b) and (c). The test is not valid unless the resolution between the peak due to phenylephrine and phenylephrine impurity F is not less than 1.5 in the chromatogram obtained with reference solution (b).the relative

standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal to noise ratio is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, The area of any peak corresponding to phenylephrine impurity C, is not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent), the area of any peak corresponding to phenylephrine citrate adduct is not more twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent). The area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 6.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.3 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Reference solution. A 0.01 per cent w/v solution of *phenylephrine hydrochloride IPRS* in the *water*.

- spectrophotometer set at 273 nm.

Inject reference solution. The test is not valid unless the tailing factor is not more than 2.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_9H_{13}NO_2$,HCI in the Injection.

Phenylephrine Hydrochloride. Page 2909

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Buffer solution. Prepared by dissolving 3.25 g of *sodium 1octanesulphonate monohydrate* in1000 ml of *water*, adjusted to pH to 2.8 with *3M orthophosphoric acid*,

Solvent mixture. 80 volumes of mobile phase A and 20 volumes of mobile phase B.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution(a). A solution containing 0.01 per cent w/v, each of, *phenylephrine hydrochloride IPRS* ,*norphenylephrine hydrochloride IPRS, phenylephrine impurity C IPRS, phenylephrine impurity D IPRS* and *phenylephrine impurity E IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution(b). A solution containing 0.1 per cent w/v of *phenylephrine hydrochloride IPRS*, 0.001 per cent w/v, each of, *norphenylephrine hydrochloride IPRS* and *phenylephrine impurity C IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 5.5 cm x 4.0 mm, packed with endcapped octadecylsilane bonded to porous silica(3 um) (Such as purospher STAR RP18e),
- column temperature: 45°,
- mobile phase: A. a mixture of 10 volumes of *acetonitrile* and 90 volumes of buffer solution,
  B. a mixture of 10 volumes of buffer solution and 90 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 10µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	93	7
3	93	7
13	70	30
14	93	7
16	93	7

Name	Relative retention time
Norphenylephrine	0.9
Phenylephrine	1.0
Phenylephrine Impurity C[1]	1.3
Phenylephrine Impurity D[2]	3.8
Phenylephrine Impurity E[3]	4.0

[1]1-(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one hydrochloride.
[2](R)-3-{2-[Benzyl(methyl)amino]-1-hydroxyethyl}phenol.
[3]2-[Benzyl(methyl)amino]-1-(3-hydroxyphenyl)ethan-1-one hydrochloride.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to norphenylephrine and phenylephrine is not less than 1.5 and between phenyephrine and phenylephrine impurity C is not less than 1.5 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 5.0 per cent for norepherine, phenylepherine, phenylephrine impurity C phenylephrine impurity D and phenylephrine impurity E in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, The area of any peak corresponding to norphenylephrine, phenylephrine impurity C, D and E, each of, is not more than the area of the corresponding peaks in the chromatogram obtained with reference solution (a) (0.10 per cent),The area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with following modifications.

Test solution. Dissolve 40 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution. A 0.04 per cent w/v solution of *phenylephrine hydrochloride IPRS* in the solvent mixture.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.9 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_9H_{13}NO_2$,HCl.

Piroxicam. Page 3295

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Note- Prepared solution immediately before use.

Test solution. Dissolve 0.1 g of the substance under examination in *methanol* with the aid of ultrasound and dilute to 100.0 ml with *methanol.*

Reference solution (a). A solution containing 0.0002 per cent w/v, each of, *piroxicam IPRS, piroxicam related compound A IPRS, piroxicam related compound D IPRS, piroxicam related compound G IPRS, piroxicam related compound J IPRS* in *methanol.*

Reference solution (b). A 0.005 per cent w/v solution of *piroxicam IPRS* in *methanol.* Dilute 1.0 ml of the solution to 100.0 ml with *methanol*.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, octadecyl silane chemically bonded to porous silica (3.5 um),
- sample temperature: 4º,
- mobile phase: A. a 0.5 per cent v/v solution of *glacial acetic acid* in *water*, adjusted to pH 6.2 with *ammonium hydroxide*,
  B. *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 235 nm (for piroxicam, piroxicam related compound A, piroxicam related compound D and any other secondary impurity)
  at 355 nm (for piroxicam related compound G and piroxicam related compound J),
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0.0	95	5
3.0	95	5
5.0	77	23
10.0	77	23
15.0	40	60
15.1	95	5
20.0	95	5

Name	Relative retention time
Piroxicam Related compound A[1]	0.35
Piroxicam Related compound G[2] (as the anhydrous form)	0.86
Piroxicam	1.0
Piroxicam Related compound B[3*]	1.2
Piroxicam Related compound D[4]	1.36
Piroxicam Related compound J[5]	1.42

[*] for peak identification only quantitated by the test for limit of piroxicam related compound B,
[1]Pyridin-2-amine,
[2]Methyl 4-hydroxy-2H-benzothiazine-3-carboxylate 1,1-dioxide monohydrate,
[3]4-Hydroxy-N-(pyridin-2-yl)-2H-benzothiazine-3-carboxamide1,1-dioxide,
[4]Methyl 2-[1,1-dioxido-3-oxobenzoisothiazol-2(3H)-yl]acetate,
[5]Methyl 4-hydroxy-2-methyl-2H-benzothiazine-3-carboxylate 1,1-dioxide.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to piroxicam and piroxicam related compound G is not less than 5.0, the relative standard deviation for replicate injections is not more than 5.0 per cent for piroxicam and piroxicam related compound A, D, G, and J in the chromatogram obtained with reference solution (a) and the signal to noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peaks corresponding to piroxicam related compound A, D, J, G, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than 0.5 times the area of principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent) and the sum of the impurities including piroxicam related compound B (from the test for limit of piroxicam related compound B) is not more than (0.4 per cent).

Insert before **Related substances**.

Limit of Piroxicam Related compound B. Determine by liquid chromatography (2.4.14).

Note- Prepared solution immediately before use.

Test solution. Dissolve 0.1 g of the substance under examination in *methanol* with the aid of ultrasound and dilute to 100.0 ml with *methanol*.

Reference solution (a). A solution containing 0.0002 per cent w/v of *piroxicam related compound B IPRS* in *methanol*.

Reference solution (b). A solution containing 0.1 per cent w/v of *piroxicam IPRS* and 0.001 per cent w/v, each of, *piroxicam related compound B IPRS* and *piroxicam related compound G IPRS* in *methanol*.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, octadecyl silane chemically bonded to porous silica (3.5 um),
- sample temperature: 4º,
- mobile phase: A. a 0.1 per cent v/v solution of *orthophosphoric acid* in *water*,
- B. *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 340 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0.0	65	35
2.0	65	35
6.0	5	95
6.1	65	35
11.0	65	35

Name	Relative retention time
Piroxicam Related compound B[1]	0.89
Piroxicam Related compound G[2]	0.95
Piroxicam	1.0

[1]4-Hydroxy-N-(pyridin-2-yl)-2H-benzothiazine-3-carboxamide1,1-dioxide,
[2]Methyl 4-hydroxy-2H-benzothiazine-3-carboxylate 1,1-dioxide monohydrate.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to piroxicam related compound B and G is not less than 1.5 in the chromatogram obtained with reference solution (b), and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution . In the chromatogram obtained with the test solution, the area of any peak corresponding to piroxicam related compound B is not more than the area of the principal peaks in the chromatogram obtained with reference solution (a) (0.2 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14) as described in limit of piroxicam Related compound B with the following modification.

Test solution. Dissolve 50 mg of the substance under examination in *methanol* and dilute to 100.0 ml with the *methanol*. Dilute 1.0 ml of the solution to 10.0 ml with *methanol*.

Reference solution. A 0.005 per cent w/v solution of *piroxicam IPRS* in *methanol.*

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{15}H_{13}N_3O_4S$.

Promethazine Hydrochloride. Page 3369

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 99.9 volumes of *methanol* and 0.1volume of *triethylamine.*

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.0005 per cent w/v solution of *promethazine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing of 0.0005 per cent w/v, each of, *promethazine hydrochloride IPRS* and *promethazine related compound B IPRS* in the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 20.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm)(Such as Luna C18 (2)),
- mobile phase: A mixture of 70 volumes of a buffer solution prepared by dissolving 3.7 g of *ammonium acetate* in1000 ml of *water* and 30 volumes of *acetonitrile,*
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.4 ml per minute,
- spectrophotometer set at 234 nm and 249 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
10	60	40
18	60	40
18.1	100	0
20	100	0

Name	Relative retention time	correction factor
Promethazine sulphoxide[1]	0.28	0.48
Desmethyl promethazine[2]	0.71	---
Promethazine	1.0	---
Promethazine related compound B[3]	1.3	---
Phenothiazine	1.7	0.5

[1]N,N-Dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine sulphoxide,
[2]N-Methyl-1-(10H-phenothiazin-10-yl)propan-2-amine,
[3]N,N-Dimethyl-2-(10H-phenothiazin-10-yl)propan-1-amine hydrochloride.

Inject reference solutions (a), (b) and (c). The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 5.0 in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injections is not more than 3.0 per cent at 234 and 249 nm in the chromatogram

obtained with reference solution (a) and the signal-to-noise ratio of the principal peak is not less than 10 at 234 and 249 nm in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution at 234 nm. In the chromatogram obtained with test solution, the area of any peak corresponding to promethazine sulphoxide is not more than 0.1 times the area of principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Inject reference solution (a) and the test solution at 249 nm. In the chromatogram obtained with test solution, the area of any peak corresponding to desmethyl promethazine is not more than 0.2 times the area of principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to promethazine related compound B is not more than 0.8 times the area of principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent), the area of any peak corresponding to promethazine is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

The sum of all the impurities (at 234 nm and 249 nm) is not more than 1.2 per cent. Ignore any peak with an area less than 0.05 times the areas of the principal peak in the chromatogram obtained at 249 nm with reference solution (a) (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. *0.1 M hydrochloric acid.*
Test solution. Dissolve 50.0 mg of the substance under examination in the solvent mixture with the aid of ultrasound and dilute to 50.0 ml with the solvent mixture. Dilute 1.0 ml of this solution to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.01 per cent w/v solution of *promethazine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing of 0.009 per cent w/v of *promethazine hydrochloride IPRS* and 0.012 per cent w/v of *promethazine related compound B IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 30 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (10 µm),
- mobile phase: mixture of 85 volumes of *acetonitrile*, 27 volumes of *water* and 0.1 volume of *triethylamine*,
- flow rate: 2.5 ml per minute,
- spectrophotometer set at 254nm,
- injection volume: 20 µl.

The relative retention time with reference to promethazine, for promethazine related compound B is about 0.82.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 1.5 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{20}N_2S$, HCl.

Propranolol Hydrochloride. Page 3377

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in 10.0 ml of the mobile phase.

Reference solution (a). A solution containing 0.2 per cent w/v of *propranolol hydrochloride IPRS* and 0.0002 per cent w/v of *propranolol impurity A IPRS* in the mobile phase.

Reference solution (b). A 0.0002 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

Reference solution (c). A 0.0001 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm),
- mobile phase: dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate* and 1.6 g of *sodium laurylsulphate* and in a mixture of 1 ml of *sulphuric acid*, 450 ml of *water* and 550 ml of *acetonitrile*, adjusted to pH 3.3 with *2 M sodium hydroxide solution,*
-flow rate: 1.8 ml per minute,
- spectrophotometer set at 292 nm,
- injection volume: 20 µl.

Name	Relative retention time	Correction factor
Propranolol impurity A[1]	0.6	0.71
Propranolol	1.0	---
Propranolol dimer[2]	4.8	0.77
Dinaphthyl glycerol[3]	5.7	0.53

[1](2RS)-3-[(naphthalen-1-yl)oxy]propane-1,2-diol,
[2]3,3′-(Isopropylazanediyl)bis[1-(naphthalen-1-yloxy)propan-2-ol],
[3]1,3-Bis(naphthalen-1-yloxy)propan-2-ol.

Inject reference solutions (a), (b) and (c). The test is not valid unless the resolution between the peaks due to propranolol and propranolol impurity A is not less than 3.0 in the chromatogram obtained with reference solution (a), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b) and signal to noise ratio for the principal peak is not less than 10.0 with reference solution (c).

Inject reference solution (b) and the test solution. Run the chromatogram 7 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any secondary peaks corresponding to propranolol impurity A, propranolol dimer and dinaphthyl glycerol, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent), the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 4.0 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (b) (0.05per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in 100.0 ml of the mobile phase.

Reference solution. A 0.02 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

Use the chromatographic system as described under Related substances.

Inject the reference solutions. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 0.73 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{16}H_{21}NO_2$.HCl.

Propranolol Injection. Page 3379

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Protect from light.

Test solution. Dilute a volume of injection containing about 0.1 g of Propranolol Hydrochloride in 100.0 ml of *acetonitrile* (if necessary).

Reference solution (a). Dilute 2.0 ml of the test solution to 500.0 ml with the mobile phase.

Reference solution (b). A solution containing 0.1per cent w/v of *propranolol IPRS* and 0.0004 per cent w/v each of, *propranolol impurity A IPRS, propranolol impurity B IPRS* and *propranolol impurity C IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil ODS),
- mobile phase: dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate* and 1.6 g of *sodium laurylsulphate* and in a mixture of 1 ml of *sulphuric acid*, 450 ml of *water* and 550 ml of *acetonitrile*, adjusted to pH 3.3 with *2 M sodium hydroxide solution*,
-flow rate: 1.8 ml per minute,
- spectrophotometer set at 292 nm,
- injection volume: 40 µl.

Name	Relative retention time
Propranolol impurity A[1]	0.6
Propranolol (Retention time: about 3 minute)	1.0
Propranolol impurity B[2]	4.5
Propranolol impurity C[3]	6.2

[1] (2RS)-3-[(naphthalen-1-yl)oxy]propane-1,2-diol,
[2] 1,1′-[(propan-2-yl)azanediyl]bis[(2≡)-3-[(naphthalen-1-yl)oxy]propan-2-ol,
[3] 1,3-bis[(naphthalen-1-yl)oxy]propan-2-ol.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to propranolol impurity A and propranolol is not less than 1.5.

Inject reference solution (a) and the test solution. Run the chromatogram 7 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with the reference solution (a) (0.1per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of injection containing about 20 mg of Propranolol Hydrochloride in 100.0 ml of *methanol.*

Reference solution (a). A 0.1per cent w/v solution of *propranolol hydrochloride IPRS* in *methanol.*

Reference solution (b). A 0.02 per cent w/v solution of *propranolol hydrochloride IPRS* in *methanol.* Pass through a suitable filter of 0.7-µm or finer pore size.

Reference solution (c). A 0.025 per cent w/v solution of *procainamide hydrochloride IPRS* in *methanol.*

Reference solution (d). Dilute 5.0 ml each of, reference solution (a) and reference solution (c) to 25.0 ml with the *methanol.*

Chromatographic system

- a stainless steel column 25 cm x4.6 mm, packed octylsilane chemically bonded to porous silica (5 µm),
- mobile phase: dissolve 0.5 g of *sodium laurylsulphate* in a 18 ml of *0.15 M phosphoric acid* add 90 ml of *acetonitrile* and 90 ml of *methanol*, dilute in 250 ml of *water*,
-flow rate: 1.5 ml per minute,
- spectrophotometer set at 290 nm,
- injection volume: 20 µl.

Inject reference solution (d).The relative retention times for procainamide and propranolol are 0.6 and 1.0.

Inject reference solutions (b) and (d). The test is not valid unless the resolution between the peaks due to procainamide and propranolol is not less than 2.0 in the chromatogram obtained with reference solution (d), the tailing factor is not more than 3.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution.

Calculate the content of $C_{16}H_{21}NO_2$.HCl in the injection.

Propranolol Prolonged-release Capsules. Page 3378

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Protect from light.

Test solution. Weigh a quantity of the mixed contents of 20 capsules containing about 0.1 g of Propranolol Hydrochloride in 100.0 ml of *methanol* mix with the aid of ultrasound for 15 minutes, shaking occasionally, and filter through glass-microfibre paper (Whatman GF/C is suitable) and use the filtrate.

Reference solution (a). Dilute 1.0 ml of the test solution to 500.0 ml with the mobile phase.

Reference solution (b). A solution containing 0.1 per cent w/v of *propranolol IPRS* and 0.0002 per cent w/v each of, *propranolol impurity A IPRS, propranolol impurity B IPRS* and *propranolol impurity C IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil ODS),
- mobile phase: dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate* and 1.6 g of *sodium laurylsulphate* and in a mixture of 1 ml of *sulphuric acid*, 450 ml of *water* and 550 ml of *acetonitrile*, adjusted to pH 3.3 with *2 M sodium hydroxide solution*,
-flow rate: 1.8 ml per minute,
- spectrophotometer set at 292 nm,
- injection volume: 40 µl.

Name	Relative retention time
Propranolol impurity A[1]	0.6
Propranolol (Retention time: about 3 minute)	1.0
Propranolol impurity B[2]	4.5
Propranolol impurity C[3]	6.2

[1] (2RS)-3-[(naphthalen-1-yl)oxy]propane-1,2-diol,
[2] 1,1′-[(propan-2-yl)azanediyl]bis[(2≡)-3-[(naphthalen-1-yl)oxy]propan-2-ol,
[3] 1,3-bis[(naphthalen-1-yl)oxy]propan-2-ol.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to propranolol impurity A and propranolol is not less than 1.5.

Inject reference solution (a) and the test solution. Run the chromatogram 7 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (a) (0.1per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 35 volumes of *acetonitrile* and 65 volumes of *water.*

Test solution. Transfer the contents of capsules to a suitable volumetric flask, disperse in *methanol* (60 per cent of the volume of the flask), and swirl by mechanical means for 2 hours. Allow to stand for 16 hours, then sonicate for 30 minutes, and swirl for 30 minutes. Dilute with *methanol* to volume, and centrifuge a portion of the solution. Use the clear supernatant for further use. Dilute suitably with solvent mixture to obtain a solution containing 0.002 per cent w/v of Propranolol Hydrochloride.

Reference solution. A 0.02 per cent w/v solution of *propranolol IPRS* in the *methanol.* Dilute 1.0 ml of this solution to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.0 mm, packed with octadecylsilane chemically bonded to porous silica (5 µm),
- mobile phase: a mixture of 35 volumes of *acetonitrile* and 65 volumes of 0.68 per cent w/v solution of *monobasic potassium phosphate,*
-flow rate: 2 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

[Note—The retention time for propranolol is about 5–9 minutes.]

Inject the reference solutions. The test is not valid unless the column efficiency is not less than 1000 theoretical plates, the tailing factor is not more than 3.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{16}H_{21}NO_2$.HCl in the capsules

Propranolol Tablets. Page 3380

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Protect from light.

Test solution. Disperse a quantity of powdered tablets containing about 0.1 g of Propranolol Hydrochloride in 100.0 ml of *methanol* and filter through glass-microfibre paper (Whatman GF/C is suitable) and use the filtrate.

Reference solution (a). Dilute 2.0 ml of the test solution to 100.0 ml with the mobile phase. Dilute 1.0 ml this solution to 10.0 ml with the mobile phase.

Reference solution (b). A solution containing 0.1per cent w/v of *propranolol IPRS* and 0.0002 per cent w/v each of, *propranolol impurity A IPRS, propranolol impurity B IPRS* and *propranolol impurity C IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil ODS 5),
- mobile phase: dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate* and 1.6 g of *sodium laurylsulphate* and in a mixture of 1 ml of *sulphuric acid*, 450 ml of *water* and 550 ml of *acetonitrile*, adjusted to pH 3.3 with *2 M sodium hydroxide solution,*
-flow rate: 1.8 ml per minute,
- spectrophotometer set at 292 nm,
- injection volume: 40 µl.

Name	Relative retention time
Propranolol impurity A[1]	0.6
Propranolol (Retention time: about 3 minute)	1.0
Propranolol impurity B[2]	4.5
Propranolol impurity C[3]	6.2

[1] (2RS)-3-[(naphthalen-1-yl)oxy]propane-1,2-diol,
[2] 1,1′-[(propan-2-yl)azanediyl]bis[(2≡)-3-[(naphthalen-1-yl)oxy]propan-2-ol,
[3] 1,3-bis[(naphthalen-1-yl)oxy]propan-2-ol.

Inject reference solutions (b). The test is not valid unless the resolution between the peaks due to propranolol impurity A and propranolol is not less than 1.5.

Inject reference solution (a) and the test solution. Run the chromatogram 7 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (a) (0.1per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described in the test for Related substances with the following modifications.

Test solution (a). Weigh and powder 20 tablets. Transfer a quantity of powder to 0.1 g of Propranolol Hydrochloride to a 100- ml volumetric flask. Add about 60 ml of mobile phase, sonicate and dilute with mobile phase to volume. Centrifuge a portion for 10 minutes, and pass the solution through a suitable filter of 0.45-µm pore size.

Test solution (b). Dilute 2.0 ml of test solution (a) to 10.0 ml with the mobile phase.

Reference solution. A 0.02 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

-injection volume: 20 µl.

[NOTE- Run the chromatogram 11 times the retention time of the principal peak.]

Inject the reference solutions. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and test solution (b).

Calculate the content of $C_{16}H_{21}NO_2$.HCl in the tablets.

Sildenafil Citrate. Page 3189

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 70 mg of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (a). A 0.00075 per cent w/v solution of *sildenafil related compound A IPRS* in the mobile phase.

Reference solution (b). Dissolve 70 mg of *sildenafil citrate IPRS* in 1 ml of a solution of *hydrogen peroxide* and *anhydrous formic acid* (2:1). Allow to stand for at least 10 minutes to generate *sildenafil N-oxide*, and then dilute with mobile phase to 250 ml.

Reference solution (c). Dilute 2.0 ml of test solution to 1000.0 ml with the mobile phase.

Reference solution (d). Dilute 5.0 ml of reference solution (c) to 20.0 ml with the mobile phase

Chromatographic system
- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Symmetry C18),
- mobile phase: a mixture of 25 volumes of *methanol*, 17 volumes of *acetonitrile* and 58 volumes of buffer solution prepared by dissolving 7 ml of *triethylamine* with *water* to 1000 ml, adjusted to pH 3.0 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 290nm,
- injection volume: 20 µl.

Name	Relative retention time
Sildenafil	1.0
Sildenafil N-oxide	1.2
Sildenafil related compound A[1]	1.7

[1]5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-(2-methylpropyl)-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
OR
[1]1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-isobutyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazine,

Inject reference solution (a) to identify the peak of sildenafil related compound A.

Inject reference solutions (b), (c) and (d). The test is not valid unless the resolution between the peaks due to sildenafil N-oxide and sildenafil is not less than 2.5 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 1.5 in the chromatogram obtained with reference solution (c) and the signal-to-noise ratio of the principal peak is not less than 10 in the chromatogram obtained with reference solution (d).

Inject reference solution (c) and the test solution. In the chromatogram obtained with test solution, the area of any peak corresponding to sildenafil related compound A is not more than 1.5 times the area of principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent). The area of any other secondary peak is not more 0.5 time than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent), the sum of areas of unspecified impurity is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent) and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to:**

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with the following modification.

Test solution. Dissolve 28 mg of the substance under examination in 100.0 ml of the mobile phase. Dilute 10.0 ml of this solution to 100.0 ml with the mobile phase.

Reference solution. A 0.0028 per cent w/v solution of *sildenafil citrate IPRS* in the mobile phase.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 0.85 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{28}H_{38}N_6O_{11}S$.

Sildenafil Tablets. Page 3190

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 90 volumes of *acetonitrile* and 10 volumes of *water.*

Test solution. Transfer 5 intact tablets in 250-m1 volumetric flask, and disperse in about 25 ml of solvent mixture with the aid of ultrasound. Cool and dilute to volume with mobile phase. Sonicate, if necessary. Centrifuge and use the supernatant. Dilute suitably with mobile phase to obtain a solution containing 0.05 per cent w/v of Sildenafil.

Reference solution (a). A mixture of *sildenafil IPRS* and *sildenafil N-oxide IPRS* in mobile phase, prepared as follows. Dissolve 70 mg of *sildenafil citrate IPRS* in 1 ml of a solution of *hydrogen peroxide* and *anhydrous formic acid* (2:1). Allow to stand for at least 10 minutes to generate *sildenafil N-oxide*, and then dilute with mobile phase to 250 ml.

Reference solution (b). A 0.00014 per cent w/v solution of *sildenafil citrate IPRS* in the mobile phase.

Reference solution (c). Dilute 5.0 ml of reference solution (b) to 20.0 ml with the mobile phase.

Chromatographic system
- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Symmetry C18),
- mobile phase: a mixture of 25 volumes of *methanol*, 17 volumes of *acetonitrile* and 58 volumes of buffer solution prepared by dissolving 7 ml of *triethylamine* with *water* to 1000 ml, adjusted to pH 3.0 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 290nm,
- injection volume: 20 µl.

Name	Relative retention time
Sildenafil	1.0
Sildenafil N-oxide[1]	1.2

[1]1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazine N4-oxide.

[NOTE- Run time: NLT 3 times the retention time of sildenafil.]

Inject reference solutions (a), (b) and (c). The test is not valid unless the resolution between the peaks due to sildenafil N-oxide and sildenafil is not less than 2.6 in the chromatogram obtained with reference solution (a), the tailing factor is not more than 1.3 and the relative standard deviation for replicate injections is not more than 3.0 per cent in the chromatogram obtained with reference solution (b). The signal-to-noise ratio of the principal peak is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (b) and the test solution. In the chromatogram obtained with test solution, the area of any peak corresponding to sildenafil N-oxide is not more than 0.71 times the area of principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any individual degradation product is not more 0.71 time than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the degradation product is not more than 1.79 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.18 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with the following modification.

Test solution. Transfer 1 intact tablet in 250-m1 volumetric flask, and disperse in about 5 ml of solvent mixture with the aid of ultrasound. Cool and dilute to volume with mobile phase. Sonicate, if necessary. Centrifuge and use the supernatant. Dilute suitably with mobile phase to obtain a solution containing 0.002 per cent w/v of Sildenafil.

Reference solution. A 0.0028 per cent w/v solution of *sildenafil citrate IPRS* in the mobile phase.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.3 and the relative standard deviation for replicate injections is not more than 3.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{30}N_6O_4S$ in the tablets.

Sulphamethoxazole. Page 3687

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution (a). Dissolve 0.1 g of the substance under examination in the mobile phase with the aid of ultrasound at 45° with intermittent shaking and dilute to 100.0 ml with the mobile phase.

Test solution (b). Dilute 1.0 ml test solution (a) to 10.0 ml with the mobile phase.

Reference solution (a). A solution containing 0.0001 per cent w/v, each of, *sulphamethoxazole IPRS* and *sulphamethoxazole related compound F IPRS* in the mobile phase. Sonicate, if necessary, to dissolve before final dilution.

Reference solution (b). A solution containing 0.0001 per cent w/v, each of, *sulphamethoxazole related compound A IPRS, sulphamethoxazole related compound B IPRS, sulphamethoxazole related compound C IPRS, sulphanilic acid IPRS* and *sulphanilamide IPRS* in the mobile phase. Sonicate, if necessary, to dissolve before final dilution.

Reference solution (c). A 0.003 per cent w/v solution of *sulphamethoxazole IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (d). A solution containing 0.01 per cent w/v, each of, *sulphamethoxazole IPRS* and *sulphamethoxazole related compound A IPRS* in the mobile phase. Sonicate at 45° with intermittent shaking to dissolve before final dilution.

Reference solution (e). A 0.001 per cent w/v solution of *sulphamethoxazole IPRS* in the mobile phase. Sonicate at 45° with intermittent shaking to dissolve before final dilution.

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with octylsilane chemically bonded to porous silica (5 µm),
- mobile phase: a mixture of 70 volumes of a buffer solution prepared by dissolve 13.6 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 5.3 with 2 per cent w/v solution of *potassium hydroxide* and 30 volumes of *methanol*,
-flow rate: 0.9 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Name	Relative retention time
Sulphanilic acid[1]	0.26
Sulphanilamide[2]	0.35
Sulphamethoxazole related compound F[3]	0.45
Sulphamethoxazole related compound C[4]	0.50
Sulphamethoxazole	1.00
Sulphamethoxazole related compound A[5]	1.20
Sulphamethoxazole related compound B[6]	2.10

[1]4-Aminobenzenesulfonic acid.
[2]4-Aminobenzenesulfonamide.
[3]4-Amino-N-(3-methylisoxazol-5-yl)benzenesulfonamide.
[4]5-Methylisoxazol-3-amine.
[5]N-{4-[N-(5-Methylisoxazol-3-yl)sulfamoyl]phenyl}acetamide.
[6]4-Amino-N-{4-[N-(5-methylisoxazol-3-yl)sulfamoyl]phenyl}benzenesulfonamide.

Inject reference solutions (b) to identify the peaks due to sulphamethoxazole related compound A, sulphamethoxazole related compound B, sulphamethoxazole related compound C, sulphanilic acid and sulphanilamide.

Inject reference solutions (a), (c) and (d). The test is not valid unless the resolution between the peaks due to sulphamethoxazole and sulphamethoxazole related compound A is not less than 3.5 in the chromatogram obtained with reference solution (d), the relative standard deviation for replicate injections is not more than 5.0 per cent for both the peaks in the chromatogram obtained with reference solution (a) and the signal to noise ratio for the principal peak is not less than 10.0 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to sulphamethoxazole related compound F is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any secondary peak corresponding to sulphanilic acid, sulphanilamide, sulphamethoxazole related compound A, B and C, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent). Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with the reference solution (a) (0.03 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under related substances with the following modifications.

The relative retention time with reference to sulphamethoxzole, for sulphamethoxazole related compound A is about 1.2.

Inject reference solutions (d) and (e). The test is not valid unless the resolution between the peaks due to sulphamethoxazole and sulphamethoxazole related compound A is not less than 3.5 in the chromatogram obtained with reference solution (d) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (e).

Inject reference solution (e) and test solution (b).

Calculate the content of $C_{10}H_{11}N_3O_3S$.

Ursodeoxycholic Acid.Page 3900

Impurity C. Change **to:**

Impurity C. Determine by liquid chromatography (2.4.14).

Buffer solution. A solution prepared dissolving 0.8 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*,adjusted to pH 3.0 with *diluteorthophosphoric acid.*

Solvent mixture A.47 volumes ofbuffer solution, 34 volumes of*methanol*and 25 volumes of*acetonitrile*.

Solvent mixture B.80 volumes ofsolvent mixtureAand 20 volumes of *methanol*.

Test solution.Dissolve 0.5 g of the substance under examination in 5 ml of *methanol*, add 30ml of solvent mixture B with the aid of ultrasound for 15 minutes and dilute to 50.0 ml with solvent mixture B.

Reference solution. A 0.01 per cent w/v solution of *lithocholic acid (impurity C) IPRS* in *methanol*.Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture B.

Chromatographic system
- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (3µm)(Such as Inertsil ODS 3),
- column temperature: 40˚,
- mobile phase: a mixture of 55 volumes of buffer solutionand 45 volumes of *acetonitrile*,
- flow rate: 0.6 ml per minute,
- refractometer detector, maintained at 40˚,
- injection volume: 100 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 andthe relative standard deviation for replicate injections is not more than 10.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to impurity C is not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances

Change **to**:**Related substances.** Determine by liquid chromatography (2.4.14).

Solvent mixture. 10 volumes of*methanol*and 90 volumes ofthe mobile phase.

Test solution. Dissolve 60 mg of the substance under examination in the solvent mixture and dilute to 20.0 ml with the solvent mixture.

Reference solution (a). A 0.003 per cent w/v solution of*ursodeoxycholic acid IPRS*in the solvent mixture.Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.00003 per cent w/v of *ursodeoxycholic acid impurityH IPRS*, 0.0003 per cent w/v of *ursodeoxycholic acid impurity A IPRS* and 0.3 per cent w/v of *ursodeoxycholic acid IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with endcapped octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40˚,
- mobile phase: a mixture of 30 volumes of *acetonitrile*,37 volumes of a 0.078 per cent w/v solution of *sodiumdihydrogen phosphate*,adjusted to pH 3.0 with *orthophosphoric acid* and 40 volumes of *methanol*,
- flow rate: 0.8 ml per minute,
- refractometer detector,maintained at 35˚,
- injection volume: 150µl.

NameRelative retention time	
Ursodeoxycholic acid impurity H[1]	0.9
Ursodeoxycholic acid (Retentiontime: about 14 minutes)	1.0
Ursodeoxycholic acid impurity A[2]	2.8

[1]3β,7β -dihydroxy-5β -cholan-24-oic acid,
[2]3α,7α -dihydroxy-5β-cholan-24-oic acid (chenodeoxycholic acid).

Inject reference solution (b) to identify the peaks due to ursodeoxycholic acid, impurity A and H.

Inject reference solution (b).The test is not valid unless the resolution between the peaks due to impurity H and ursodeoxycholic acid is not less than 1.5.

Inject reference solution (a) and the test solution. Run the chromatogram 4 times the retention time of the principal peak, the area of any peak corresponding toursodeoxycholic impurity A is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 15times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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Insert before **Related substances**

Impurity C. Determine by liquid chromatography (2.4.14).

Buffer solution. A solution prepared dissolving 0.8 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*,adjusted to pH 3.0 with *diluteorthophosphoric acid.*

Solvent mixture A.47 volumes ofbuffer solution, 34 volumes of *methanol* and 25 volumes of*acetonitrile*.

Solvent mixture B.80 volumes ofsolvent mixtureAand 20 volumes of *methanol*.

Test solution.Dispersea quantity of powdered tablets containing 0.5 g of ursodeoxycholic acidin 5 ml of *methanol*, add 30 ml of solvent mixture B with the aid of ultrasound for 15 minutes and dilute to 50.0 ml with solvent mixture B.

Reference solution. A 0.01 per cent w/v solution of *lithocholic acid (impurity C) IPRS* in *methanol*.Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture B.

Chromatographic system
- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (3µm) (Such as Inertsil ODS 3),
- column temperature: 40˚,
- mobile phase: a mixture of 55 volumes of buffer solutionand 45 volumes of *acetonitrile*,
- flow rate: 0.6 ml per minute,
- refractometer detector, maintained at 40˚,
- injection volume: 100 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 andthe relative standard deviation for replicate injections is not more than 10.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to impurity C is not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances
Change**to**:**Related substances.** Determine by liquid chromatography (2.4.14).

Solvent mixture. 20 volumes of*methanol*and 80 volumes of mobile phase.

Test solution.Disperse a quantity of the powdered tablets containing 0.25 g of Ursodeoxycholic acidin the solvent mixture with the aid of ultrasound for 15 minutes and dilute to 50.0 ml with the solvent mixture and filter.

Reference solution (a). A 0.0025 per cent w/v solution of*ursodeoxycholic acid IPRS*in the solvent mixture.

Reference solution (b). A solution containing 0.5 per cent w/v of *ursodeoxycholic acid IPRS*, 0.0025 per cent w/v*ursodeoxycholic acid impurity F IPRS (7-ketolithocholic acid)*, 0.0055 per cent w/v of *ursodeoxycholic acid impurity A IPRS (chenodeoxycholic acid)* in the solvent mixture.

Reference solution (c). Dilute 1.0 ml of the reference solution (a) to 10.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (3 µm),(Such asUptisphere HDO C_{18}),
– column temperature: 40˚,
– mobile phase: a mixture of 25 volumes of *acetonitrile*,34 volumes of *methanol* and 47 volumes of a buffer solution prepared by dissolving 0.8 g of *sodium dihydrogen orthphosphosphate dihydrate* in 1000 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid*,
– flow rate: 0.6 ml per minute,
– refractometer detector,maintained at 40˚,
– injection volume: 8 µl.

Name	Relative retention time
Ursodeoxycholic acid (Retention time: about 5 minutes)	1.0
Ursodeoxycholic acid impurity F[1]	1.3
Ursodeoxycholic acid impurity A[2]	2.8

[1]7-ketolithocholic acid
[2]chenodeoxycholic acid

Inject reference solution (b) to identify the peaks due to ursodeoxycholic acid, impurity A and F.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to ursodeoxycholicacid and ursodeoxycholic acid impurity Fis not less than 2.0.

Inject reference solution(a),(c) and the test solution.Run the chromatogram 5 times the retention time of the principal peak, the area of any peak corresponding toursodeoxycholic acid impurity A is not more than 3 times the area of the principal peakin the chromatogram obtained with reference solution (a)(1.5 per cent), the area of anyother secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of areas of all the secondary peaks is not more than 4.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.1 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).