INDIAN PHARMACOPOEIA COMMISSION

MINISTRY OF HEALTH & FAMILY WELFARE, GOVERNMENT OF INDIA
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No. T.11013/02/2018-AR&D **Dated:25 May, 2018**

To,

1. **Drugs Controller General (India)/CDSCO, Zonal Offices**
2. **All State Drug Controllers**
3. **Members of Scientific Body of the IPC**
4. **Members of Sub-Committee of Scientific Body of the IPC**
5. **Government Analysts**
6. **Director of Drugs Testing Laboratories**
7. **IDMA/OPPI/BDMA/FSSAI/Small Scale Industry Associations**

AMENDMENT LIST– 002 to IP-2018

As you are aware that 8th edition of Indian Pharmacopoeia has been effective from 1st January, 2018. Further, the effective date has been relaxed/ extended till 30th June, 2018 for the stakeholders who could not upgrade/ changed their products for compliance of IP- 2018.

Based on Scientific inputs, some monographs needed up-gradation; accordingly an Amendment List- 002 is issued containing such amendments.

This is for notice and compliance with IP-2018.

(Dr. G.N. Singh)
Secretary-cum-Scientific Director

Encl:- Amendment List – 002 for IP-2018

AMENDMENT LIST 002 to IP-2018

5.4. Residual Solvents. Page 986

Appendix 1. List of solvents included in the guideline

Under Class of Cumene

Change **from**: Class 3

to: Class 2

Under Class of Methylisobutylketone

Change **from**: Class 3

to: Class 2

Insert the following, after 1,1,2-Trichloroethene.

Solvent	Other Names	Structure	Class
Triethylamine	*N,N*-Diethylethanamine	$N(CH_2CH_3)_3$	Class 3

Dried Aluminium Hydroxide. Page 1185

Microbial Contamination (2.2.9).

Change **from**: Total aerobic viable count is not more than 10^2 CFU per ml determined by plate count. 1 ml is free from *Escherichia coli*.

to: Total aerobic viable count is not more than 10^3 CFU and total fungal count is not more than 10^2CFU per g determined by plate count. 1g is free from *bile-tolerant gram-negative bacteria* and *Escherichia coli*.

Aminophylline Tablets. Page 1209

Para 1.

Change **from**: Aminophylline Tablets contain theophylline, $C_7H_8N_4O_2$, equivalent to not less than 80.6 per cent and not more than 90.8 per cent of the stated amount of aminophylline, and ethylenediamine, $C_2H_8N_2$, equivalent to not less than 10.9 per cent and not more than 12.1 per cent of the stated amount of aminophylline.

to: Aminophylline Tablets contain theophylline, $C_7H_8N_4O_2$, equivalent to not less than 81.4 per cent and not more than 90.0 per cent of the stated amount of aminophylline, and ethylenediamine, $C_2H_8N_2$, equivalent to not less than 13.5 per cent and not more than 15.0 per cent of the stated amount of aminophylline.

Atorvastatin and Fenofibrate Tablets. Page 1289

Dissolution(2.5.2).

Reference solution.

Change **from**: Weigh a suitable quantity of *atorvastatin calcium RS* and *fenofibrate RS* and transfer to a 50.0 ml volumetric flask. Dissolve with about 30 ml of *methanol* and dilute to volume with *methanol*. Dilute suitable volume with the dissolution medium to obtain a solution having a known concentration similar to the concentration of the test solution.

to: *Reference solution(a)*.Weigh accurately about 55 mg of *atorvastatin calcium RS* in a 50 ml volumetric flask, add 30.0 ml of *methanol,* sonicate and make up the volume with *methanol.*

Reference solution (b).Weigh accurately about 80 mg of *fenofibrate RS* in a 25-ml volumetric flask, add 15 ml of *methanol,* sonicate and make up the volume with *methanol.*

Reference solution (c). Dilute a suitable volume of reference solution (a) and reference solution (b) with dissolution medium to obtain a solution having similar concentration to the test solution.

Inject reference solution (c) and the test solution.

Uniformity of Content. *For tablets containing 10 mg or less of Atorvastatin -*

Test solution.

Change **from**: Disperse one tablet in 30 ml of *methanol*, sonicate for 15 minutes, dilute to 50.0 ml with same solvent, centrifuge at 2500 rpm for about10 minutes, and filter. Dilute 5.0 ml of this solution to 25.0 ml with the mobile phase.

to: Disperse 1 tablet in 10 ml of *water* with the aid of ultrasound. Add about 30 ml of *methanol* and disperse with aid of ultrasound for 15 minutes, cool and dilute to 50.0 ml with *methanol* and mix. Centrifuge at 2500 rpm for 10 minutes, rejecting the first few ml of filtrate. Dilute 5.0 ml of this solution to 25.0 ml with the mobile phase.

Assay. Determine by liquid chromatography (2.4.14).

Test solution.

Change **from**: Weigh and powder 20 tablets. Disperse a quantity of the powder containing 160 mg of Fenofibrate with 60 ml of *methanol* sonicate for 15 minutes, dilute to 250.0 ml with the same solvent centrifuge at 2500 rpm for about 10 minutes, and filter. Dilute 10.0 ml of the filtrate to 25.0 ml with the mobile phase.

to: Weigh and powder 20 tablets. Disperse a quantity of powdered tablets containing 200 mg of Fenofibrate into a 250-ml volumetric flask, add 100 ml of *methanol* and sonicate for 25 minutes with intermittent shaking. Make up the volume with *methanol*, mix and centrifuge. Dilute 4.0 ml of clear supernatant to 10.0 ml with mobile phase.

Reference solution

Change **from**: *Reference solution(a)*. A 0.18 per cent w/v solution of *atorvastatin calcium RS* in *methanol.* Dilute 5.0 ml of this solution to 50.0 ml with *methanol*.

Reference solution (b). A 0.064 per cent w/v solution of *fenofibrateRS* in *methanol*.

Reference solution (c).Dilute 5.0 ml reference solution (a) and 10.0 ml of reference solution (b) to 25.0 ml with the mobile phase.

to: *Reference solution(a)*.Weigh accurately about 60 mg of *atorvastatin calcium RS* in a 50-ml volumetric flask, add 30 ml of *methanol* sonicate it to dissolve and make up the volume with *methanol.*

Reference solution(b).Weigh accurately about 80 mg of *fenofibrate RS* in a 25-ml volumetric flask, add 15 ml of *methanol* sonicate it to dissolve and make up the volume with *methanol.*

Reference solution (c). Dilute 2.0 ml reference solution (a) and 5.0 ml of reference solution (b) to 50.0 ml with the mobile phase.

Bendamustine Hydrochloride. Page 1334

Insert the following, below Molecular formula and Molecular weight,

$C_{16}H_{24}Cl_3N_3O_3$ Mol Wt. 412.7

Water (2.3.43).

Change **to:** Not more than 0.5 per cent for the anhydrous form and 4.5 to 6.5 per cent for the monohydrate form determined on 0.1 gm.

Bisoprolol Fumarate and Hydrochlorothiazide Tablets. Page 1393

Dissolution.

Reference solution (b).

Change **from**: A 0.06 per cent w/v solution of *hydrochlorothiazide RS* in dissolution medium.

to: Weigh 30 mg of *hydrochlorothiazide RS* in 50 ml volumetric flask, dissolve in 5 ml of *methanol* and dilute to volume with dissolution medium.

Related substances.

Reference solution. Line 2

Change **from:** *bisoprolol fumarate RS*

to: *hydrochlorothiazide RS*

After chromatographic system. Para 1, lines 1 and 2.

Change **from:** 1.2

to: 0.83

Change **from:** 1.4

to: 0.71

Para 2, line 3, 4 and 5

Change **from:** peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (2.0 per cent). The area of any other secondary peak is not more than.…

to: peak at relative retention time of 1.2 is not more than the area of the principal peak in the chromatogram obtained with the reference solution (2.0 per cent). The area of any other secondary peak at relative retention time of 0.69 is not more than…….

Insert at the end.

Calculate the percentage of each impurity using following expression:

$$100 \times C \times \frac{Lb}{Lh} \times \frac{Cs}{Cb} \times \frac{Rt}{Rs}$$

Where, C= Correction factor for the peak with relative retention time of 0.69 and 1.2,
Lb = Labelled quantity of bisoprolol fumarate in mg,
Lh = Labelled quantity of hydrochlorothiazide in mg,
Cs= Concentration of *hydrochlorothiazide RS* in reference solution (mg per ml),
Cb= Concentration of bisoprolol fumarate in test solution (b) (mg per ml),
Rt= Peak area of each of the two impurity obtained from test solution (b),
Rs= Peak area of hydrochlorothiazide peak obtained from reference solution.

Assay. Under chromatographic system

- Mobile phase B. Line 2

Change **from:** add 10 ml of *1 M dibutyl ammonium phosphate*…….
to: add 0.5 volume of *1 M dibutyl ammonium phosphate*……

Dibasic Calcium Phosphate. Page1464

Loss on ignition. Line 3

Change **from**: 500°
to: 800° - 825°

Calcium and Vitamin D_3 Tablets. Page 1466

Identification B.

Change **from**: Disperse a quantity of powdered tablets containing 10 mg of calcium in 50 ml of *water* and filter. It gives the reaction (A) of calcium salts (2.3.1).
to: Disperse a quantity of powdered tablets containing 10 mg of calcium in 5 ml of *water* and add 5 ml of *5 M acetic acid* or 1 ml of *glacial acetic acid* and filter. It gives the reaction (A) of calcium salts (2.3.1).

Uniformity of content.

Test solution.

Change **from**: Disperse one tablet in 8 ml of *methanol* with the aid of ultrasound for 15 minutes, dilute to 10.0 ml with *methanol*, mix and centrifuge. Use the supernatant liquid.
to: Disperse one tablet in 2.5 ml of *water* by shaking for 5 minutes. Add about 15 ml of *methanol* and sonicate for 20 minutes with intermittent shaking and dilute to 25.0 ml with *methanol*, mix and centrifuge the solution at 4000 rpm for 5 minutes and filter. Dilute the filtrate, if necessary, with the *methanol*.

Reference solution.

Change **from**: A 0.00005 per cent w/v solution of *cholecalciferol RS* in the *methanol*.
to: A 0.000025 per cent w/v solution of *cholecalciferol RS* in the *methanol (90 per cent, v/v)*.

Assay. *For Vitamin D_3 (Cholecalciferol) —*

Test solution.

Change **from**: Weigh and powder 20 tablets. Disperse a quantity of powdered tablets equivalent to 0.1 mg of vitamin D_3 in 170 ml of *methanol* by shaking for 5 minutes and mix with ultrasound for 5 minutes, dilute to 200.0 ml with *methanol*, mix and filter. Use the filtrate.
to: Weigh and powder 20 tablets. Disperse a quantity of powdered tablets equivalent to 0.1 mg of vitamin D_3 in 20 ml of *water* by shaking for 5 minutes. Add about 120 ml of *methanol* and sonicate for 20 minutes with intermittent shaking and dilute to 200.0 ml with *methanol*, mix and centrifuge the solution at 4000 rpm for 5 minutes and filter. Use the filtrate.

Reference solution.

Change **from**: A 0.00005 per cent w/v solution of *cholecalciferol RS* in the *methanol*.

to: A 0.00005 per cent w/v solution of *cholecalciferol RS* in the *methanol(90 per cent, v/v)*.

Chromatographic system, lines 1 and 2

Change **from**: – a stainless steel column 10 cm x 4.6 mm, packed with octadecylsilane bonded to silica polymer (5 µm),

to: – a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),

Chlorpheniramine Maleate. Page1596

Identification

Change **to**:

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

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.

Daunorubicin Injection. Page 1767

Assay. *Test solution*.

Change **from**: Determine the weight of the contents of 10 containers. Dissolve a weighed quantity of the mixed contents of 10 containers containing about 25 mg daunorubicin to 100.0 ml with the mobile phase.

to: Reconstitute 1 vial with 5 ml of mobile phase and transfer to 200-ml volumetric flask. Wash the vial twice with 5 ml of mobile phase and transfer to the same volumetric flask. Repeat the same procedure for another 9 vials and dilute to volume. Further dilute 5.0 ml of this solution to 20.0 ml with the mobile phase.

Disodium Edetate. Page 1858

Impurity A. Change **to**:

Impurity A. Determine by liquid chromatography (2.4.14).

Note- Carry out the test protected from light.

Solvent A. A 1.0 per cent w/v solution of *cupric nitrate* in *water*.

Test solution. Dissolve 100 mg of the substance under examination in 10.0 ml of solvent A and sonicate to dissolve.

Reference solution (a). Transfer 100 mg of *nitrilotriacetic acid* to a 10-ml volumetric flask, add 0.5 ml of *ammonium hydroxide*, mix, and dilute with *water* to volume.

Reference solution (b). Transfer 1g of disodium edetate to a 100-ml volumetric flask, add 100 µl of reference solution (a), dilute with solvent A and sonicate to dissolve.

Reference solution (c). Transfer 10 mg of disodium edetate to a 100-ml volumetric flask, add 100 µl of reference solution (a), dilute with solvent A and sonicate to dissolve.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (1.5 to 10 µm),
- mobile phase: a mixture of solution prepared by diluting 10 volumes of *1M tetrabutylammonium hydroxide* in *methanol* to 200.0 ml with *water,* adjusted to pH 7.5 ± 0.1 with *dilute orthophosphoric acid* and 90 volumes of *methanol* and dilute to 1000 ml with *water*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 50 µl.

The relative retention time with reference to edetate for nitrilotriacetic acid and copper is about 0.35 and 0.65, respectively.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to nitrilotriacetic acid and copper is not less than 3.0 in the chromatogram obtained with reference solution (c) 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. In the chromatogram obtained with the test solution the area of peak corresponding to nitrilotriacetic acid is not more than difference between the area of nitrilotriacetic acid peak obtained from reference solution (b) and the test solution (0.1 per cent).

Disulfiram Tablets. Page 1862

Identification C. Delete the requirement.

Drospirenone and Ethinylestradiol Tablets. Page 1908

Dissolution (2.5.2). Last para

Change **from**: D. Not less than 85 per cent of the stated amounts of $C_{24}H_{30}O_3$ and not less than 75 per cent of the stated amount of $C_{20}H_{24}O_2$.

to: D. Not less than 80 per cent of the stated amount of $C_{24}H_{30}O_3$ and not less than 75 per cent of the stated amount of $C_{20}H_{24}O_2$.

Ethylcellulose. Page 2004

Assay. Change **to**:

Assay. Determine by gas chromatography (2.4.13).

Internal standard solution. To 10 ml of *o-xylene* add 0.5 ml of *octane* and dilute to 100.0 ml with *o-xylene*.

Test solution. To 30 mg (dried substance), add 60 mg of *adipic acid* in a 5 ml pressure–tight reaction vial equipped with a pressure-tight membrane stopper coated with *polytetrafluoroethylene* and secured with an aluminium crimped cap or another sealing system providing a sufficient air-tightness. Add 2.0 ml of the internal standard solution and 1.0 ml of *hydriodic acid* and close immediately. Accurately weigh the vial (total mass before heating), do not mix the contents of the vial by hand before heating. Place the vial in an oven or heat in a suitable heater, with continuous mechanical agitation, maintaining the internal temperature of the vial at 115± 2° for 70 minutes. Allow to cool and accurately weigh the vial (total mass after heating). If the difference between the total mass before heating and the total mass after heating is more than 10 mg, prepare a new test solution. After phase separation, pierce through the septum of the vial with a cooled syringe and withdraw a sufficient volume of the upper layer as the test solution.

Reference solution. Place 60 mg of *adipic acid* and 2.0 ml of the internal standard solution in another 5 ml reaction vial, add 1.0 ml of *hydriodic acid* and close immediately. Accurately weigh the vial then inject 25µl of *iodoethane* through the septum into the vial, weigh again accurately and mix. After phase separation, pierce through the septum of the vial with a cooled syringe and withdraw a sufficient volume of the upper layer as the reference solution.

Chromatographic system

- a fused silica column 30 m x 0.53 mm, packed with poly (dimethyl) siloxane (film thickness 3 µm),
- temperature:

column	time (min)	temprature (°)
	0-3	50
	3-8	50→100
	8-12	100→250
	12-20	250

- inlet port at 250° and detector at 280°,
- flow rate: 4.2 ml per minute using helium as carrier gas,
- flame ionization detector,
- split ratio: 1:40.

The relative retention time with reference to octane (retention time about 10 minutes) iodoethane about 0.6.

Inject 1µl of the reference solution. The test is not valid unless the resolution between the peaks due to iodoethane and octane is not less than 5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and internal standard solution.

Calculate the response factor of iodoethane using the following expression.

$$\frac{A_1 x W_1 x C}{A_2 x 100}$$

A_1= area of the peak due to the internal standard in the chromatogram obtained with the reference solution,
A_2 = area of the peak due to iodoethane in the chromatogram obtained with the reference solution,
W_1= mass of iodoethane in the reference solution in mg,
C = percentage content of iodoethane.

Inject the reference solution, internal standard solution and the test solution.

Calculate the percentage content m/m of ethoxy groups using the following expression.

$$\frac{A_4 x\ R x\ M_1 x\ 100}{A_3 x W_2 x M_2}$$

A_3 = area of the peak due to the internal standard in the chromatogram obtained with the test solution,
A_4= area of the peak due to iodoethane in the chromatogram obtained with the test solution,
R = reponse factor
M_1= molar mass of the ethoxygroups (45.1)
M_2= molar mass of iodoethane (156.0)
W_2= mass of the sample (dried substance) in the test solution, in mg.

Guaiphenesin. Page 2197

Guaiacol. Delete the requirement.

Hyoscine Butylbromide Injection. Page 2248

Bacterial endotoxins (2.2.3).

Change **to:** Not more than 8.75 Endotoxin Units per mg of hyoscine butylbromide.

Metformin Hydrochloride Prolonged-release and Glimepiride Tablets. Page 2546

Identification

Change **from**: In the Assay, the principal peaks in the chromatogram obtained with the test solution correspond to the principal peaks in the chromatogram obtained with the reference solution.

to: A. When examined in the range of 200-300 nm, a 0.001 per cent w/v solution of *metformin hydrochloride RS* and test solution, as obtained in the Assay, shows absorption maxima, at about 232 nm (2.4.7).

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

Assay *For Glimepiride-*

Test solution.

Change **from**: Weigh and powder 20 tablets. Disperse a quantity of the powder containing 1 mg of Glimepiride in 20 ml of solvent mixture with the aid of ultrasound and dilute to 25.0 ml with the same solvent.

to: Disperse intact tablets in solvent mixture with the aid of ultrasound to produce a solution containing 0.004 per cent w/v of Glimepiride.

Methylcobalamin. Page 2561

Para 1.

Change **from**: Mecobalamine contains not less than 98.0 per cent of $C_{63}H_{91}CoN_{13}O_{14}P$, calculated on the anhydrous basis.

to: Mecobalamine contains not less than 98.0 per cent and not more than 102.0 per cent of the stated amount of $C_{63}H_{91}CoN_{13}O_{14}P$, calculated on the anhydrous basis.

Miconazole Cream. Page 2607

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *methanol* and *tetrahydrofuran*.

Test solution. Shake a quantity of the cream containing about 50 mg of Miconazole Nitrate with 30 ml of the solvent mixture for 30 minutes, dilute to 50.0 ml with the solvent mixture and filter.

Reference solution (a). A 0.1 per cent w/v solution of *miconazole nitrate RS* in the solvent mixture.

Reference solution (b). A 0.0025 per cent w/v solution each of *miconazole nitrate RS* and *econazole nitrate RS* in the solvent mixture.

Use chromatographic system as described under Related substances.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to miconazole and econazole is not less than 10.

Inject reference solution (a) and test solution.

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

Noscapine.Page 2756

Para 2

Change **from**: Noscapine contains not less than 98.5 per cent and not more than 100.5 per cent of $C_{22}H_{23}N0_7$, calculated on the dried basis.

to: Noscapine contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{22}H_{23}N0_7$, calculated on the dried basis.

Olopatadine Ophthalmic Solution. Page 2780

Related substances. A.

After chromatographic system, para 1, lines 5 to 9.

Change **from**: the tailing factor is not more than 2.0, the column efficiency is not less than 2000 theoretical plates and the relative standard deviation for replicate injections is not more than 2.0 per cent for principal peak obtained with reference solution (b).

to: 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 for principal peak obtained with reference solution (b).

B.

After mobile phase, para 1, lines 5 to 9.

Change **from**: the tailing factor is not more than 2.0, the column efficiency is not less than 2000 theoretical plates and the relative standard deviation for replicate injections is not more than 2.0 per cent for principal peak obtained with reference solution (b).

to: 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 for principal peak obtained with reference solution (b).

Assay. After *Reference solution*, para 1, lines 1 to 4.

Change **from**: 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 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

to: 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.

Oxybutynin Hydrochloride. Page 2817

Add Synonym. After title.

Oxybutynin Chloride

Pantoprazole Gastro-resistant Tablets. Page 2849

Para 1

Change **from**: Pantoprazole Gastro-resistant Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of pantoprazole, $C_{16}H_{15}F_2N_3O_4S$. They are made gastro-resistant by enteric-coating or by other means.

to: Pantoprazole Gastro-resistant Tablets contain an amount of Pantoprazole sodium equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of pantoprazole, $C_{16}H_{15}F_2N_3O_4S$. They are made gastro-resistant by enteric-coating or by other means.

Proguanil Tablets. Page 3012

Add the following before **4-Chloroaniline**.

Dissolution (2.5.2).

Apparatus No. 1,
Medium. 900 ml of *0.2 M hydrochloric acid* containing 0.2 per cent w/v solution of *sodium chloride*,
Speed and time. 50 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter. Dilute a suitable volume of the filtrate, if necessary with dissolution medium. Measure the absorbance of the resulting solution at the maximum at about 242 nm (2.4.7), Calculate the content of $C_{11}H_{16}ClN_{5,}HCl$ in the medium from the absorbance obtained from a solution of known concentration of *proguanil hydrochloride RS.*

D. Not less than 75 per cent of the stated amount of $C_{11}H_{16}ClN_{5,}HCl$.

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets. Weigh a quantity of the powder containing 100 mg of Proguanil Hydrochloride, dissolve in 50 ml of *methanol* and shake for 10 minutes, dilute to 100.0 ml with *methanol*. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

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

Reference solution (b). Mix 1.0 ml of 0.05 per cent w/v solution of *1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride RS* in *methanol* and 9 ml of 0.01per cent w/v solution of *proguanil hydrochloride RS* in the mobile phase.

Chromatographic system

- a stainless steel column 10 cm x 5.0 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil C18),
- column temperature: 40º,
- mobile phase: dissolve 1.89 g of *sodium hexanesulphonate* in a mixture of 500 ml of *methanol*, 500 ml of *water* and 5 ml of *glacial acetic acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Inject the reference solution (b). The test is not valid unless the chromatogram shows two clearly separated peaks due to proguanil hydrochloride and 1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride.

Inject reference solution (a) and test solution. The sum of the areas of any secondary peaks in the chromatogram obtained with test solution is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets.Weigh a quantity of the powder containing 100 mg of Proguanil Hydrochloride, dissolve in 50 ml of *methanol* and shake for 10 minutes, dilute to 100.0 ml with *methanol*. Dilute 5.0 ml to 50.0 ml with *methanol*. Dilute 10.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution(a). A 0.002 per cent w/v solution of *proguanil hydrochloride RS* in the mobile phase.

Reference solution(b). Mix 1.0 ml of 0.05 per cent w/v solution of *1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride RS* in *methanol* and 9 ml of 0.01per cent w/v solution of *proguanil hydrochloride RS* in the mobile phase.

Use chromatographic system as described under Related substances.

Inject reference solution (b). The test is not valid unless the chromatogram shows two clearly separated peaks due to proguanil hydrochloride and 1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{11}H_{16}ClN_{5,}HCl$.

Rosuvastatin and Fenofibrate Tablets. Page 3144

Identification. Line 3

Change **from**: reference solution

to: reference solution (c)

Dissolution (2.5.2) Lines 6 to 8.

Change **from**: Determine by liquid chromatography (2.4.14), using the chromatographic system described under Assay, using 50µl as injection volume.

to: Determine by liquid chromatography (2.4.14), using the chromatographic system, solvent mixture and system suitability criteria as described under Assay.

Reference solution.

Change **from**: *Reference solution*. Dissolve a quantity of *rosuvastatin calcium RS* and *fenofibrate RS* in mobile

Phase and dilute with the dissolution medium to obtain a solution having a known concentration similar to the test solution.

to: *Reference solution(a)*. A 0.052 per cent w/v solution of *rosuvastatin calcium RS* in solvent mixture.

Reference solution (b). A 0.016 per cent w/v solution of *fenofibrate RS* in solvent mixture.

Reference solution (c). Dilute a suitable volume of reference solution (a) and (b) with dissolution medium, to obtain a solution having concentration similar to the test solution.

Uniformity of Content. *For tablets containing 10 mg or less*.

Test solution.

Change **from**: Disperse one tablet in 60 ml of solvent mixture, ultrasound for 10 minutes, dilute to 100.0 ml with mobile phase, mix and centrifuge. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

to: Disperse 1 tablet in 10 ml of *water* with the aid of ultrasound. Add about 30 ml of solvent mixture and disperse with aid of ultrasound for 15 minutes. Further add 30 ml of mobile phase and disperse with aid of ultrasound for 25 minutes, cool and dilute to 100.0 ml with mobile phase, mix and centrifuge at 2500 rpm for 10 minutes. Rejecting the first few ml of filtrate, dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution.

Change **from**: A 0.012 per cent w/v solution of *rosuvastatin calcium RS* in solvent mixture. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

to: A 0.012 per cent w/v solution of *rosuvastatin calcium RS* in the solvent mixture and dilute to volume with mobile phase to obtain a solution having similar concentration to the test solution.

Assay. Determine by liquid chromatography (2.4.14).

Test solution.

Change **from**: Weigh and powder 20 tablets. Disperse a quantity of the powdered tablets containing 160 mg of Fenofibrate with 60 ml of solvent mixture with the aid of ultrasound for 10 minutes, dilute to 100.0 ml with mobile phase, mix and centrifuge. Dilute 5.0 ml of this solution to 50.0 ml with mobile phase.

to: Weigh and powder 20 tablets. Disperse a quantity of powdered tablets containing 800 mg of Fenofibrate into a 250-ml volumetric flask, add 125 ml of solvent mixture and sonicate for 25 minutes with intermittent shaking. Dilute to volume with the mobile phase, mix and centrifuge. Dilute 5.0 ml of clear supernatant to 50.0 ml with the mobile phase.

Reference solution.

Change **from**: *Reference solution* . A 0.012 per cent w/v solution of *rosuvastatin calcium RS* and 0.16 per cent w/v solution of *fenofibrate* RS in the mobile phase. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

to: *Reference solution(a)*. A 0.052 per cent w/v solution of *rosuvastatin calcium RS* in the solvent mixture.

Reference solution(b). A 0.032 per cent w/v solution of *fenofibrate RS* in solvent mixture.

Reference solution (c). Dilute a suitable volume of reference solution (a) and (b) with mobile phase, to obtain a solution having concentration similar to the test solution.

After chromatographic system. lines 1 and 4.

Change **from**: reference solution

to: reference solution (c)

Sertaconazole Nitrate. Page 3182

Related substances. Last para, lines 5 to 7

Change **from**: B and C are not more than 2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent),

to: B and C are not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent), the relative retention time of impurity C, impurity B and impurity A are about 0.12, 0.18 and 0.3 respectively,

Telmisartan and Amlodipine Tablets. Page 3321

Dissolution. (2.5.2)

Change **to**:

Dissolution (2.5.2).

For Amlodipine-

Apparatus No. 1,

Medium. 500 ml *0.01 M hydrochloric acid,*

Speed and time.75 rpm and 20 minutes.

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 0.001 per cent w/v solution of*amlodipine besylate RS* in dissolution medium.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica(5µm),
- autosampler temperature: 10º,

- mobile phase: a mixture of 60 volumes of a buffer solution prepared by dissolving *0.022*g *monobasic sodium phosphate dihydrate* and 2 ml of *triethylamine* in 1000 ml of *water* and adjusted to pH 6.0 with *orthophosphoric acid* and 40 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 257 nm,
- injection volume: 20 µl.

Inject the 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 $C_{20}H_{25}ClN_2O_5$.

D. Not less than 80 per cent of the stated amount of $C_{20}H_{25}ClN_2O_5$.

For Telmisartan-
Apparatus No. 1,
Medium. 900 ml of *phosphate buffer pH 7.5*, prepared by dissolving *0.05 M of monobasic potassium phosphate* and *0.038 M sodium hydroxide* in 1000 ml of *water*, adjusted to pH 7.5 with *dilute sodium hydroxide*,
Speed and time.75 rpm and 20 minutes.
Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Solvent mixture. Add 5 volumes of *triethylamine* in 500 volumes of *water* and further add 500 volumes of *acetonitrile* and mix.

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

Reference solution. A 0.1 per cent w/v solution of *telmisartan RS* in solvent mixture. Dilute 5.0 ml of this solution to 100.0 ml with the dissolution medium.

Use chromatographic system as described under dissolution of Amlodipine.

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 $C_{33}H_{30}N_4O_2$.

D. Not less than 80 per cent of the stated amount of $C_{33}H_{30}N_4O_2$.

Related substances.
After chromatographic system, last para, line 7
Change **from**: amlodipine
to: telmisartan

Line 10
Change **from**: amlodipine
to: telmisartan

Lines 11 to 14
Change **from**: Ignore any peaks with an area less than 0.5 times the principal peak as the chromatogram obtained with reference solution (c) (0.05 per cent).
to: Ignore any peaks with an area less than 0.5 times of telmisartan peak in chromatogram obtained with reference solution (c) (0.05 per cent).

Telmisartan and Hydrochlorothiazide Tablets. Page 3323

Related Substances, *Reference solution (d)*.
Line 1
Change **from**: 0.000125
to: 0.0025
Line 6, insert at the end.
for telmisartan 40 mg and hydrochlorothiazide 12.5 mg and 0.000025 percent w/v for telmisartan 80 mg and hydrochlorothiazide 12.5 mg.
Reference solution (e). Line 4
Change **from**: reference solution (a)

to: 0.0025 per cent w/v solution of *benzothiadiazine impurity A* RS in the solvent mixture.

Assay. *Reference Solution (a)*.
Change **to**: A 0.32 percent w/v solution of *telmisartan RS* in the solvent mixture.
Reference Solution (b).
Change **to**: A 0.05 percent w/v solution of *hydrochlorothiazide RS* in the solvent mixture.
Reference Solution (c).
Change **to**: Dilute a suitable volume of reference solution (a), reference solution (b) and 0.0025 per cent w/v solution of *benzothiadiazine impurity A* in solvent mixture in equal volumes of mobile phase A and mobile phase B to obtain a solution having similar concentration to the test solution and 0.00005 per cent w/v solution of *benzothiadiazine impurity A*.

Terbinafine Cream. Page 3337

pH. Delete the requirement

Tobramycin. Page 3386

Para 2
Change **from**: Tobramycin has potency not less than 930 Units per mg, calculated on anhydrous and 2-methyl-1-propanol-free basis.
to: Tobramycin has potency not less than 900 mcg of $C_{18}H_{37}N_5O_9$ per mg, calculated on anhydrous basis.