# INDIAN PHARMACOPOEIA COMMISSION

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**Date:** 03.06.2020

05/06/2020

To,

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

**Subject: Amendment List-05 to IP 2018**

The 8th Edition of Indian Pharmacopoeia (IP) 2018 has become effective from 1st January, 2018. Based on scientific inputs, some IP monographs needed up-gradation and accordingly Amendment List - 05 to IP 2018 is issued containing such amendments.

This is for notice and compliance with IP 2018.

05/06/2020

**(Dr. Jai Prakash)**
**Secretary-cum-Scientific Director (I/c)**

**Encl.** Amendment List-05 to IP 2018

# Amendment List 05 to IP-2018

## Allopurinol. Page 1176

**Heavy metals**

Change **to: Heavy metals** (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

## Bisacodyl Gastro-resistant Tablets. Page 4419

**Dissolution** A. After chromatographic system, line 2

Change **from:** Calculate the content of $C_{22}H_{19}NO_4$ in the medium.

**to:** Calculate the content of $C_{22}H_{19}NO_4$.

Complies with the acceptance criteria given under acid stage.

## Calcium Gluconate. Page 1458

**Dose.** Line 3

Change **from:** 2.3mmol

**to:** 2.3mEq

## Calcium Gluconate Injection. Page 1459

**Usual strengths.** Line 4

Change **from:** 0.45mmol

**to:** 0.45mEq

## Citicoline Injection. Page 1639

Para 2

Change **to:** Citicoline Injection contains Citicoline Sodium equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of citicoline, $C_{14}H_{26}N_4O_{11}P_2$.

**Assay**. Last line

Change **from:** $C_{14}H_{25}N_4O_{11}P_2$

**to:** $C_{14}H_{26}N_4O_{11}P_2$

## Citicoline Prolonged-release Tablets. Page 1639

Para 2

Change **to:** Citicoline Prolonged-release Tablets contain Citicoline Sodium equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of citicoline, $C_{14}H_{26}N_4O_{11}P_2$.

**Assay.** Last line

Change **from:** $C_{14}H_{25}N_4O_{11}P_2$

**to:** $C_{14}H_{26}N_4O_{11}P_2$

## Citicoline Tablets. Page 1641

Para 2

Change **to:** Citicoline Tablets contain Citicoline Sodium equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of citicoline, $C_{14}H_{26}N_4O_{11}P_2$.

**Assay.** Last line

Change **from:** $C_{14}H_{25}N_4O_{11}P_2$

**to:** $C_{14}H_{26}N_4O_{11}P_2$

## Ipratropium Bromide. Page 2305

Para 2, line 2

Change **from:** $C_{20}H_{30}BrNO_3$, $H_2O$

**to:** $C_{20}H_{30}BrNO_3$,

**Water**

Change **from:** Not more than 5.0 per cent, determined on 0.5 g.

**to:** 3.9 per cent to 4.4 per cent, determined on 0.5 g.

## Kanamycin Injection. Page 2347

***A. Kanamycin Injection (Solution),*** Para 1

Change **to**: Kanamycin Injection contains Kanamycin Sulphate equivalent to not less than 97.0 per cent and not more than 110.0 per cent of the stated number of Units of kanamycin.

Insert before **Bacterial endotoxins**

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

## Lamivudine and Zidovudine Tablets. Page 2381

**Related substances**

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

*Solvent mixture*. 95 volumes of mobile phase A and 5 volumes of mobile phase B.

*Test solution*. Disperse a quantity of the powdered tablets containing 150 mg of Lamivudine in *water* with the aid of ultrasound for 15 minutes and dilute to 100.0 ml with *water*, filter. Dilute 1.0 ml of the filtrate to 10.0 ml with the solvent mixture.

*Reference solution (a)*. A solution containing 0.015 per cent w/v of *lamivudine RS* and 0.03 per cent w/v of *zidovudine RS* in the solvent mixture.

*Reference solution (b)*. A 0.017 per cent w/v solution of *lamivudine resolution mixture B RS* in the 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 Inertsil ODS-3v),
- mobile phase: A. a buffer solution prepared by dissolving 1.95 g of *ammonium acetate* in 900 ml of *water*, adjusted to pH 4.0 with *glacial acetic acid* and dilute to 1000.0 ml with *water*,
  B. *methanol*,
  C. *acetonitrile*,
- flow rate: 1ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 270 nm,
- injection volume: 10 µl.

| Time (in min.) | Mobile phase A (per cent v/v) | Mobile phase B (per cent v/v) | Mobile phase C (per cent v/v) |
|---|---|---|---|
| 0 | 95 | 5 | 0 |
| 15 | 95 | 5 | 0 |
| 30 | 70 | 30 | 0 |
| 38 | 70 | 30 | 0 |
| 38.1 | 0 | 0 | 100 |
| 45 | 0 | 0 | 100 |
| 45.1 | 95 | 5 | 0 |
| 60 | 95 | 5 | 0 |

| Name | Relative retention time | Correction factor | Acceptance Criteria Not more than (per cent) |
|---|---|---|---|
| Lamivudine-(cytosine)[1.11] | 0.11 | --- | --- |
| Lamivudine-(uracil)[2.11] | 0.14 | --- | --- |
| Lamivudine-(carboxylic acid)[11] | 0.17 | --- | 0.3 |
| Lamivudine-(S-sulphoxide)[3.11] | 0.20 | --- | --- |
| Lamivudine-(R-sulphoxide)[4.11] | 0.22 | --- | --- |

| | | | |
|---|---|---|---|
| Zidovudine impurity C[5] | 0.27 | 0.59 | 1.5 |
| Lamivudine diastereomer[6] | 0.50 | --- | 0.2 |
| Lamivudine | 0.52 | --- | --- |
| Zidovudine-(thymidine)[7,11] | 0.60 | --- | --- |
| Lamivudine-(uracil derivative)[8, 11] | 0.70 | --- | --- |
| Lamivudine-(salicylic acid)[9, 11] | 0.80 | --- | --- |
| Zidovudine | 1.0 | --- | --- |
| Zidovudine impurity B[10, 11] | 1.1 | --- | --- |
| Any other secondary impurity | --- | --- | 0.1 |
| Total lamivudine related impurities | --- | --- | 0.6 |
| Total zidovudine related impurities (The limit includes other impurities) | --- | --- | 2.0 |

[1] 4-Aminopyrimidin-2(1*H*)-one,
[2] Pyrimidine-2,4(1*H*,3*H*)-dione,
[3] 1-[(2*R*,3*S*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine S-oxide,
[4] 1-[(2*R*,3*S*,5*SS*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine S-oxide,
[5] 5-Methylpyrimidine-2,4(1*H*,3*H*)-dione,
[6] 1-[(2*S*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine,
[7] [1-(2-Deoxy-β-d-ribofuranosyl)]thymine,
[8] (2*R*,5*S*)1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]uracil,
[9] 2-Hydroxybenzoic acid,
[10] 3'-Chloro-3'-deoxythymidine.
[11] These are the process related impurities, monitored in the drug substance,

The relative retention time for lamivudine diastereomer and lamivudine are 0.5 and 0.52 respectively.

Inject reference solution (a) and (b). The test is not valid unless the resolution between lamivudine diastereomer and lamivudine peaks is not less than 1.5 in the chromatogram obtained with reference solution (b) and the relative standard deviation of replicate injections is not more than 2.0 per cent for each component in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the percentage of each lamivudine related impurity in the portion of tablets taken:

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

$r_U$ = peak response of each lamivudine related impurity from the test solution
$r_T$ = sum of the peak responses of lamivudine and all lamivudine related impurities from the test solution

Calculate the percentage of each zidovudine related impurity and other impurity in the portion of tablets taken:

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

$r_U$ = peak response of each zidovudine related impurity and other secondary impurity from the test solution
$r_T$ = sum of the peak responses of zidovudine, all zidovudine related impurities and other impurities from the test solution
$c$ = correction factor

## Lithium Carbonate. Page 2449

**Potassium**

Change **from:** Dissolve 1.0 g in 10 ml of 7 *M hydrochloric acid,* add sufficient *water* to produce 50 ml and determine by flame photometry (2.4.4), measuring at 766.5 nm, using *potassium solution FP,* suitably diluted with *water,* to prepare the standard solutions (500 ppm).

**to:** Dissolve 1.0 g in 10 ml of 7 *M hydrochloric acid,* add sufficient *water* to produce 50 ml and determine by Method A of flame photometry (2.4.4) or by Method A for Atomic absorption spectrophotometry (2.4.2), measuring at 767 nm, using *potassium solution FP* or *potassium solution AAS* respectively, suitably diluted with *water,* to prepare the standard solutions (500 ppm).

**Sodium**
Change **from:** Dissolve 1.0 g in 10 ml of *7 M hydrochloric acid,* add sufficient *water* to produce 50 ml and determine by flame photometry (2.4.4), measuring at 589 um, using *sodium solution FP,* suitably diluted with *water,* to prepare the standard solutions (500 ppm).

**to:** Dissolve–1.0 g in 10 ml of *7 M hydrochloric acid,* add sufficient *water* to produce 50 ml and determine by Method A for flame photometry (2.4.4) or by Method A for atomic absorption spectrophotometry (2.4.2), measuring at 589 nm, using *sodium solution FP* or *sodium solution AAS* respectively, suitably diluted with *water,* to prepare the standard solutions (500 ppm).

## Malic Acid. Page 2493
**Specific optical rotation.** Line 1
Change **from: Specific optical rotation**
**to: Optical rotation**

## Nortriptyline Tablets. Page 2755
**Uniformity of content.** Last line
Change **from:** $C_{20}H_{23}N$
**to:** $C_{19}H_{21}N$

Insert after **Storage**
**Labelling.** The label states the strength in terms of equivalent amount of nortriptyline.

## Nystatin. Page2759
**Composition.** Last para, line 7
Insert after reference solution (a).

Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

**Abnormal toxicity**
**Delete** the following requirement

*Nystatin intended for oral administration complies with the following additional requirements.*
**Abnormal toxicity** (2.2.1). Complies with the test for abnormal toxicity, using a quantity containing not less than 600 Units suspended in not more than 0.5 ml of a 0.5 per cent w/v solution of *acacia* and injecting the suspension intraperitoneally.

## Ormeloxifene Hydrochloride Tablets. Page 2795
**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 the reference solution.

## Pantoprazole Gastro-resistant and Domperidone Prolonged-release Capsules.
Page 2850
**Dissolution**
*For Pantoprazole Sodium.* A. After chromatographic system, line 6
Change **From**: Calculate the content of $C_{16}H_{15}F_2N_3O_4S$.
**to:** Calculate the content of $C_{16}H_{15}F_2N_3O_4S$ released in the acid medium by subtracting the content of $C_{16}H_{15}F_2N_3O_4S$ in the test solution from the total content of Pantoprazole, $C_{16}H_{15}F_2N_3O_4S$ determined in the Assay.

## Polyvinyl Alcohol. Page 2960
Insert at the end
**Labelling.** The label states (1) viscosity in terms of mPas (2) ester value.

## Prednisolone Tablets. Page 2980

**Assay**

*Reference solution (b)*

Change **to:** *Reference solution (b).* A 0.005 per cent w/v solution of *prednisolone RS* in a mixture of 58 volumes of *methanol* and 42 volumes of *water.*

## Raloxifene Hydrochloride. Page 3085

**Assay.** After chromatographic system, para 1

Change **to:** Inject reference solution (a) and (b).The test is not valid unless the resolution between the raloxifene-N-oxide and principal peak is not less than 2.0 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 0.7 per cent in the chromatogram obtained with reference solution (a).

## Raloxifene Hydrochloride Tablets. Page 3087

**Dissolution.** After chromatographic system, line 2

Change **from:** tablet.

**to:** medium.

**Assay.** After chromatographic system, para 1

Change **to:** Inject reference solution (a) and (b).The test is not valid unless the resolution between the raloxifene-N-oxide and principal peak is not less than 2.0 in the chromatogram obtained with reference solution (a), 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 (b).

## Ropinirole Prolonged-release Tablets. Page 4501

**Related substances.** After chromatographic system, para 1, line 5 and 6

Change **from:** not more than 10.0 per cent for ropinirole impurity B in the chromatogram

**to:** not more than 10.0 per cent in the chromatogram

## Streptomycin Sulphate. Page 3265

Para 2

Change **to**: Streptomycin Sulphate has a potency equivalent to not less than 720 µg of streptomycin per mg, calculated on the dried basis.

## Sulbactam Sodium. Page 4513

**Related substances**

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

*Buffer solution.* A 0.27 per cent w/v solution of *monobasic potassium phosphate,* adjusted to pH 4.0 with *orthophosphoric acid.*

*Solvent mixture.* 98 volumes of the buffer solution and 2 volumes of *acetonitrile.*

*Test solution.* Dissolve 77 mg of the substance under examination in 2 ml of *acetonitrile* and dilute to 100.0 ml with the buffer solution.

*Reference solution (a).* Dissolve 70 mg of *sulbactam RS* in 2 ml of *acetonitrile* and dilute to 100.0 ml with the buffer solution.

*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).* A solution containing 0.007 per cent w/v each of *sulbactam related substance A RS, sulbactam related substance D RS, sulbactam related substance E RS* and *sulbactam related substance F RS* in *acetonitrile*. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture (*NOTE- Protect the solution from light*).

Chromatographic system

- a stainless steel column 15 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (3 µm),
- column temperature: 40°,
- mobile phase: A. a 0.54 per cent w/v solution of *monobasic potassium phosphate,* adjusted to pH 4.0 with *orthophosphoric acid,*
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 20 µl.

| Time (in min) | Mobile phase A (per cent v/v) | Mobile phase B (per cent v/v) |
|---|---|---|
| 0 | 98 | 2 |
| 7.5 | 50 | 50 |
| 8.5 | 50 | 50 |
| 9.0 | 98 | 2 |
| 13 | 98 | 2 |

| Name | Relative retention time | Correction factor |
|---|---|---|
| Sulbactam related compound A[1] | 0.4 | 0.59 |
| Amoxicillin related compound A[2] | 0.6 | 0.50 |
| Sulbactam | 1.0 | - |
| 6-Bromopenicillanic acid sulfone[3] | 1.6 | - |
| Sulbactam related compound D[4] | 2.0 | 0.5 |
| Sulbactam related compound E[5] | 2.1 | - |
| Sulbactam related compound F[6] | 2.5 | 0.59 |

[1]3-Sulfino-D-valine; (2*S*)-2-Amino-3-methyl-3-sulfinobutanoic acid.
[2]6-Aminopenicillanic acid; (2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
[3](2*S*,5*R*,6*R*)-6-Bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide.
[4]6-Bromopenicillanic acid; (2*S*,5*R*,6*R*)-6-Bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
[5]6,6-Dibromopenicillanic acid sulfone; (2*S*,5*R*)-6,6-Dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide.
[6]6,6-Dibromopenicillanic acid; (2*S*,5*R*)-6,6-Dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Inject reference solution (b) and (c). The test is not valid unless the resolution between sulbactam related compound D and sulbactam related compound E peaks is not less than 1.5 in the chromatogram obtained with reference solution (c) 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. In the chromatogram obtained with the test solution, the area of any peak corresponding to sulbactam related compound A is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any peak corresponding to 6-bromopenicillanic acid sulfone and sulbactam related compound E, each of is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any peak corresponding to amoxicillin related compound A, sulbactam related compound D and sulbactam related compound F, 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 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 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0

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).

## Terazosin Tablets. Page 3334

**Related substances**

*Reference solution (a)*

Change **from:** A 0.0003 per cent w/v solution of *terazosin hydrochloride RS* in the mobile phase.

**to:** A solution of *terazosin hydrochloride RS* in the mobile phase to obtain 0.0003 per cent w/v of terazosin.

Last para, line 4 and 5

Change **from:** any peak due to piperazinyl-ADMQ, chloro ADMQ and bis-ADMQ piperazine

**to:** any peak corresponding to piperazinyl-ADMQ, chloro ADMQ and bis-ADMQ piperazine, each of,

## Trimethobenzamide Hydrochloride. Page 3439

**Assay.** Line 5

Change **from:** 0.04299 g

**to:** 0.04249 g