DRAFT REVISIONS FOR COMMENTS

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This draft proposal contains general chapter/monographs text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to arnd-ipc@gov.in , with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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Further follow-up action as required.	

Index of Proposed Revisions

S. No.	Name of General Chapter/ Monograph	Details of Proposed Revision	Revision
1.	2.1.7. Balances used in Analytical Procedures	Repeatability: Minor amendment	**1.0**
2.	2.4.26. Solubility: Minoxidil	Upgrade solubility	**1.0**
3.	2.4.50. Chromatographic Separation Techniques	Upgrade Equation	**1.0**
4.	4.2 General Reagents	Insert Clozapine *N*-Oxide Phenanthroline Solution	**1.0**
5.	Abacavir and Lamivudine Tablets	Insert Labelling	**1.0**
6.	Abacavir, Lamivudine and Zidovudine Tablets	Insert Labelling	**1.0**
7.	Acetylcysteine Injection	Related substances: RRT table Minor amendment	**1.0**
8.	Aciclovir	Related substances: Upgrade Reference solution (d)	**1.0**
9.	Aciclovir Cream	Related substances: Upgrade Reference solution (d)	**1.0**
10.	Aciclovir Dispersible Tablets	Related substances: Upgrade Reference solution (d)	**1.0**
11.	Aciclovir Eye Ointment	Related substances: Upgrade Reference solution (d)	**1.0**
12.	Aciclovir for Intravenous Infusion	Related substances: Upgrade Reference solution (d)	**1.0**
13.	Aciclovir Oral Suspension	Related substances: Upgrade Reference solution (d)	**1.0**
14.	Aciclovir Tablets	Related substances. Upgrade Reference solution (d)	**1.0**
15.	Alprazolam	Upgrade Identification	**1.0**
16.	Amiloride Hydrochloride	Free acid. Minor amendment	**1.0**
17.	Amlodipine and Benazepril Hydrochloride Capsules	Related substances: Reference solution (b) Minor amendment	**1.0**
18.	S-Amlodipine Besylate	Upgrade Water Limit	**1.0**
19.	Amoxycillin for Injection	Delete Other tests	**1.0**
20.	Arteether	Identification Minor amendment	**1.0**
21.	Aspirin Tablets	Upgrade Dissolution Apparatus	**1.0**
22.	Atazanavir Capsules	Insert Labelling	**1.0**
23.	Atomoxetine Hydrochloride	Para 2, Upgrade Sulphated ash limit, water changed into Loss on drying	**1.0**
24.	Azilsartan Kamedoxomil	Related substances: Upgrade Reference solution (a), (b) and Impurity B limit	**1.0**
25.	Azilsartan Tablets	Dissolution, Assay and Related substances: Minor amendment	**1.0**
26.	Barium Sulphate for Suspension	Upgrade Other tests	**1.0**
27.	Beclomethasone Dipropionate	Related substances: Upgrade Reference solution (a)	**1.0**
28.	Bedaquiline Tablets	Upgrade Identification, Insert Labelling	**1.0**
29.	Benazepril Hydrochloride Tablets	Assay: Insert Flow rate	**1.0**
30.	Bendamustine for Injection	Related substances: Minor amendment	**1.0**
31.	Benzathine Penicillin	Upgrade Structure	**1.0**
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34.	Compound Benzoin Tincture	Insert Other tests	**1.0**
35.	Betamethasone Dipropionate	Insert Sulphated ash	**1.0**
36.	Betamethasone Sodium Phosphate	Upgrade Identification	**1.0**
37.	Betamethasone Sodium Phosphate Tablets	Assay: Minor amendment	**1.0**
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39.	Betaxolol Eye Drops	Assay: Upgrade SST requirement	**1.0**
40.	Bicalutamide	Delete Specific optical rotation and Insert Sulphated ash	**1.0**
41.	Bumetanide	Upgrade Identification, Related substances, Assay and Storage	**1.0**
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44.	Bumetanide Tablets	Upgrade Identification, Related substances, Assay and Insert Storage	**1.0**
45.	Buprenorphine Injection	Related substances: Upgrade Reference solution (a)	**1.0**
46.	Caffeine	Loss on drying: Minor amendment	**1.0**
47.	Calcium Orotate	pH and Assay: Minor amendment	**1.0**
48.	Dibasic Calcium Phosphate, Anhydrous	Upgrade Identification	**1.0**
49.	Dibasic Calcium Phosphate, Dihydrate	Upgrade Identification	**1.0**
50.	Carbamazepine	Upgrade Identification	**1.0**
51.	Carisoprodol	Insert Sulphated ash	**1.0**
52.	Cefadroxil	Correct misprinting in Identification and Insert Sulphated ash	**1.0**
53.	Cefpodoxime for Oral Suspension	Assay: Upgrade Reference solution	**1.0**
54.	Cetrimide Emulsifying Ointment	Para 2: Minor amendment	**1.0**
55.	Chlorothiazide Tablets	Correct misprinting in Assay	**1.0**
56.	Chloroxylenol	Correct misprinting in Assay	**1.0**
57.	Chlorpheniramine Maleate	Related substances: Minor amendment	**1.0**
58.	Chlorpromazine Hydrochloride	Identification: Minor amendment	**1.0**
59.	Cilastatin Sodium	Insert Sterility	**1.0**
60.	Ciprofloxacin Tablets	Assay: Upgrade Reference solution (a)	**1.0**
61.	Cisplatin Injection	Minor amendment	**1.0**
62.	Clarithromycin	Related substances: Upgrade Impurity limit	**1.0**
63.	Clarithromycin Tablets	Related substances: Upgrade Impurity limit	**1.0**
64.	Clindamycin Palmitate Hydrochloride for Oral Solution	Assay: Minor amendment	**1.0**
65.	Clobetasol Propionate	Related substances: Upgrade Reference solution (c)	**1.0**
66.	Clomipramine Hydrochloride	Assay: Minor amendment	**1.0**
67.	Cloxacillin Sodium	Upgrade Water Limit	**1.0**
68.	Cloxacillin for Oral Solution	Insert Other tests	**1.0**
69.	Codeine Phosphate	Upgrade Loss on drying limit	**1.0**
70.	Cyproheptadine Hydrochloride	Delete Para 2, Related substances: Reference solution (a) Minor amendment	**1.0**
71.	Hard Cellulose Capsule Shells	Upgrade Arsenic, Disintegration. Minor amendment	**1.0**
72.	Clozapine	Complete Revision	**1.0**
73.	Clozapine Tablets	Complete Revision	**1.0**
74.	Dapagliflozin and Metformin Hydrochloride Prolonged-release Tablets	Upgrade Dissolution	**1.0**
75.	Dasatinib	Related Substances: Minor amendment	**1.0**
76.	Daunorubicin for Injection	Insert Labelling	**1.0**
77.	Dextrose	Upgrade Identification A	**1.0**
78.	Dicloxacillin Capsules	Insert Labelling	**1.0**
79.	Dicloxacillin for Oral Suspension	Other tests: Minor amendment	**1.0**
80.	Ferric Carboxymaltose	Zeta potential: Minor amendment	**1.0**
81.	Fexofenadine Hydrochloride	Chlorides: Minor amendment	**1.0**
82.	Finasteride	Related substances: Minor amendment	**1.0**
83.	Fructose	Complete Revision	**1.0**

84.	Fructose Injection	Upgrade Assay	**1.0**
85.	Frusemide	Assay: Minor amendment	**1.0**
86.	Fulvestrant	Enantiomeric purity: Typoerror correct	**1.0**
87.	Gelatin	Peroxides: Minor amendment	**1.0**
88.	Hydrochlorothiazide	Assay: Minor amendment	**1.0**
89.	Hydrocortisone Sodium Succinate for Injection	Related substances. Upgrade Reference solution (b)	**1.0**
90.	Hydroxyethyl Cellulose	Nitrates: Minor amendment	**1.0**
91.	Hyoscine Butylbromide	Related substances. Reference solution (a) typoerror correct	**1.0**
92.	Levetiracetam Prolonged -release Tablets	Related substances: Upgrade RRT table	**1.0**
93.	Levetiracetam Tablets	Related substances: Upgrade RRT table	**1.0**
94.	Levonorgestrel	Upgrade Related substances	**1.0**
95.	Methylergometrine Maleate	Upgrade Identification, Assay and Storage	**1.0**
96.	Methylergometrine Injection	Upgrade Assay and Storage	**1.0**
97.	Methylergometrine Tablets	Insert Dissolution and Upgrade Assay	**1.0**
98.	Minocycline Hydrochloride	Related substances: Minor amendment	**1.0**
99.	Minocycline Capsules	Related substances: Minor amendment	**1.0**
100.	Minocycline Tablets	Related substances: Minor amendment	**1.0**
101.	Minoxidil	Complete Revision	**1.0**
102.	Minoxidil Tablets	Complete Revision	**1.0**
103.	Neotame	Related substances: Minor amendment	**1.0**
104.	Montelukast Sodium	Related substances: Minor amendment	**1.0**
105.	Nifedipine	Related substances: Minor amendment	**1.0**
106.	Nitrofurantoin	Upgrade Water into Loss on drying	**1.0**
107.	Paracetamol	Related substances: Typoerror corrected	**1.0**
108.	Phenytoin Tablets	Insert Dissolution	**1.0**
109.	Pralidoxime Chloride	Complete Revision	**1.0**
110.	Pralidoxime Chloride for Injection	Complete Revision	**1.0**
111.	Pregabalin Capsules	Related substances. Minor amendment	**1.0**
112.	Prochlorperazine Maleate	Complete Revision	**1.0**
113.	Prochlorperazine Tablets	Complete Revision	**1.0**
114.	Ramipril Capsules	Related substances: Minor amendment	**1.0**
115.	Ramipril Tablets	Related substances: Minor amendment	**1.0**
116.	Rosuvastatin Calcium	Related substances: Minor amendment	**1.0**
117.	Rosuvastatin Tablets	Related substances: Typoerror corrected	**1.0**
118.	Sertraline Tablets	Related substances and Assay: Typoerror corrected	**1.0**
119.	Sodium Valproate Oral Solution	Upgrade Related substances and Assay	**1.0**
120.	Sodium Valproate Gastro -resistant Tablets	Upgrade Related substances	**1.0**
121.	Sodium Valproate Tablets	Upgrade Dissolution, Related substances and Assay	**1.0**
122.	Sorbitol	Upgrade Nickel	**1.0**
123.	Tenofovir Disoproxil Fumarate Tablets	Related substances: Reference solution (a) Typoerror corrected	**1.0**
124.	Triprolidine Hydrochloride	Complete Revision	**1.0**
125.	Triprolidine Tablets	Complete Revision	**1.0**
126.	Ursodeoxycholic Acid	Identification. B: Typoerror corrected	**1.0**
127.	Vildagliptin and Metformin Prolonged -release Tablets	Related substances: Minor amendment	**1.0**
128.	Xanthan Gum	Viscosity: Typoerror corrected	**1.0**
VETERINARY PRODUCTS			
129.	Ampicillin Injection	Title Change	**1.0**
130.	Moxidectin	Related substances: Minor amendment	**1.0**
131.	Moxidectin Injection	Insert Related substances	**1.0**

2.1.7. Balances used in Analytical Procedures. Page 25

Repeatability. Equation 4

Change **from**: $Mmin = 200 \times s$

to: $Mmin = 2000 \times s$

2.4.26. Solubility. Page 290

Minoxidil. Page 311

Change **to: Minoxidil**. Soluble in *ethanol (95 per cent)* and in *propylene glycol*; sparingly soluble in *methanol*; slightly soluble in *water*; practically insoluble in *chloroform*, in *acetone*, in *ethyl acetate*, and in *hexane*.

2.4.50. Chromatographic Separation Techniques. Page 386

Page 389

Resolution. Equation 1

Change **from**: $\frac{Rs=1.18\ (t_{R2}-tR1)}{Wh1-Wh2}$

to: $\frac{Rs=1.18\ (t_{R2}-tR1)}{Wh1+Wh2}$

Page 392

System Repeatability. Equation

Change **from**: *per cent* RSD $= \frac{100}{y}\sqrt{\frac{\Sigma\,(yi-\overline{y})}{n-1}}$

to: *per cent* RSD $\frac{100}{y}\sqrt{\frac{\Sigma\,(yi-\overline{y})^2}{n-1}}$

4.2 General Reagents. Page 1176

Page 1196

Insert before **Cobalt Acetate**

Clozapine *N*-Oxide; (8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine N-oxide): $C_{18}H_{19}ClN_4O$ 342.82

Use a suitable grade with a content of not less than 98 per cent.

Page 1231

Phenanthroline Hydrochloride. Insert at the end

Phenanthroline Solution: Dissolve 1.5 g of *1,10-phenanthroline* in sufficient *water* to produce 100 ml.

4.5. Volumetric Reagents and Solutions

Page 1286

Zinc Sulphate, 0.02 M, Line 1

Change **from**: 4.88 g

to: 5.76 g

Abacavir and Lamivudine Tablets. Page 1496

Insert at the end

Labelling. The label states the strength in terms of the equivalent amount of Abacavir and Lamivudine.

Abacavir, Lamivudine and Zidovudine Tablets. Page 1497

Insert at the end

Labelling. The label states the strength in terms of the equivalent amount of Abacavir, Lamivudine and Zidovudine.

Acetylcysteine Injection. Page 1519

Related substances. RRT table

Insert after line 3

Acetylcysteine impurity C[3]	2.2

Insert at the end

[3]3,3'-disulphanediylbis[(2*R*)-2-acetamidopropanoic acid] (*N, N'*-diacetyl-*L*-cystine).

Aciclovir. Page 1521

Related substances. *Reference solution (d)*

Change **from**: Dissolve the content of a vial of *aciclovir for impurity G identification IPRS* in 1 ml of reference solution (b).

to: Dissolve 0.002 mg of *aciclovir impurity G IPRS* in 1 ml of reference solution (b).

Aciclovir Cream. Page 1522

Related substances. *Reference solution (d)*

Change **from**: Dissolve the content of a vial of *aciclovir for impurity G identification IPRS* in 1 ml of reference solution (b).

to: Dissolve 0.002 mg of *aciclovir impurity G IPRS* in 1 ml of reference solution (b).

Aciclovir Dispersible Tablets. Page 1524

Related substances. *Reference solution (d)*

Change **from**: Dissolve the content of a vial of *aciclovir for impurity G identification IPRS* in 1 ml of reference solution (b) (*NOTE ─ Prepare the solution immediately before use*).

to: Dissolve 0.002 mg of *aciclovir impurity G IPRS* in 1 ml of reference solution (b) (*NOTE ─ Prepare the solution immediately before use*).

Aciclovir Eye Ointment. Page 1525

Related substances. *Reference solution (d)*

Change **from**: Dissolve the content of a vial of *aciclovir for impurity G identification IPRS* in 1 ml of reference solution (b) (*NOTE ─ Prepare the solution immediately before use*).

to: Dissolve 0.002 mg of *aciclovir impurity G IPRS* in 1 ml of reference solution (b) (*NOTE ─ Prepare the solution immediately before use*).

Aciclovir for Intravenous Infusion. Page 1527

Related substances. *Reference solution (d)*

Change **from**: Dissolve the content of a vial of *aciclovir for impurity G identification IPRS* in 1 ml of reference solution (b).

to: Dissolve 0.002 mg of *aciclovir impurity G IPRS* in 1 ml of reference solution (b).

Aciclovir Oral Suspension. Page 1528

Related substances. *Reference solution (d)*

Change **from**: Dissolve the content of a vial of *aciclovir for impurity G identification IPRS* in 1 ml of reference solution (b).

to: Dissolve 0.002 mg of *aciclovir impurity G IPRS* in 1 ml of reference solution (b).

Aciclovir Tablets. Page 1530

Related substances. *Reference solution (d)*

Change **from**: Dissolve the content of a vial of *aciclovir for impurity G identification IPRS* in 1 ml of reference solution (b).

to: Dissolve 0.002 mg of *aciclovir impurity G IPRS* in 1 ml of reference solution (b).

Alprazolam. Page 1558

Identification. Change **to**:

Identification

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

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.

Amiloride Hydrochloride. Page 1585

Free acid. Insert at the end
Carry out a blank titration.

Amlodipine and Benazepril Hydrochloride Capsules. Page 1612

Related substances. *Reference solution (b)*, line 2
Change **from**: *amlodipine besylate IPRS*
to: *amlodipine besylate IPRS* equivalent to amlodipine

S-Amlodipine Besylate. Page 1621

Water. Line 1
Change **from**: Not more than 8.0 per cent
to: 6.5 per cent to 8.0 per cent

Amoxycillin for Injection. Page 1630

Other tests. Delete the requirement.

Arteether. Page 1671

Identification. Para 1
Delete the requirement.

Aspirin Tablets. Page 1684

Dissolution. Line 1
Change **from**: Apparatus 2 (paddle)
to: Apparatus 1 (basket)

Atazanavir Capsules. Page 1696

Insert at the end
Labelling. The label states the strength in terms of the equivalent amount of atazanavir.

Atomoxetine Hydrochloride. Page 1703

Para 2, line 3
Change **from**: calculated on the anhydrous basis.
to: calculated on the dried basis.

Sulphated ash
Change **from**: Not more than 0.2 per cent.
to: Not more than 0.1 per cent.

Water
Change **to**: **Loss on drying** (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying under vacuum at 105° for 2 hours.

Azilsartan Kamedoxomil. Page 1731

Related substances. *Reference solution (a),* line 1 and 2
Change **from**: A 0.00562 per cent w/v solution of *azilsartan medoxomil IPRS*
to: A 0.006 per cent w/v solution of *azilsartan kamedoxomil IPRS*

Reference solution (b). Line 2
Change **from**: *azilsartan medoxomil IPRS*
to: *azilsartan kamedoxomil IPRS*

After impurity table, para 3, lines 10 to 13
Change **from**: the area of any peak corresponding to azilsartan kamedoxomil impurity B is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent).
to: the area of any peak corresponding to azilsartan kamedoxomil impurity B is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent).

Assay. *Reference solution*
Change **from**: A 0.0225 per cent w/v solution of *azilsartan medoxomil IPRS* in the solvent mixture.
to: A 0.023 per cent w/v solution of *azilsartan kamedoxomil IPRS* in the solvent mixture.

Azilsartan Tablets. Page 1733
Dissolution. *Reference solution,* line 1 and 2
Change **from**: A 0.09 per cent w/v solution of *azilsartan medoxomil IPRS* in *acetonitrile*.
to: A solution of *azilsartan kamedoxomil IPRS* in *acetonitrile* containing 0.09 per cent w/v of azilsartan medoxomil.

Related substances. *Reference solution.* Line 1 and 2
Change **from**: A 0.002 per cent w/v solution of *azilsartan medoxomil IPRS* in *acetonitrile*.
to: A solution of *azilsartan kamedoxomil IPRS* in *acetonitrile* containing 0.002 per cent w/v of azilsartan medoxomil.

Assay. *Reference solution.* Line 1 and 2
Change **from**: A 0.005 per cent w/v solution of *azilsartan medoxomil IPRS* in the mobile phase.
to: A solution of *azilsartan kamedoxomil IPRS* in the mobile phase containing 0.005 per cent w/v of azilsartan medoxomil.

Barium Sulphate for Suspension. Page 1761
Other tests
Change **from**: Comply with the tests stated under Oral Liquids.
to: Comply with the tests stated under Oral Powders.

Beclomethasone Dipropionate. Page 1762
Related substances. *Reference solution (a)*, line 2 and 3
Change **from**: 2.8 ml of mobile phase A and dilute to 10.0 ml with mobile phase B.
to: 5.6 ml of mobile phase B and dilute to 10.0 ml with mobile phase A.

Bedaquiline Tablets. Page 1766
Identification. A
Change **to**: A. Take a quantity of the powdered tablets containing 2 mg of bedaquiline, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *bedaquiline fumarate IPRS* or with the reference spectrum of bedaquiline fumarate.

Insert at the end
Labelling. The label states the strength in terms of the equivalent amount of bedaquiline.

Benazepril Hydrochloride Tablets. Page 1770
Assay. Chromatographic system, insert before line 5
- flow rate: 1 ml per minute,

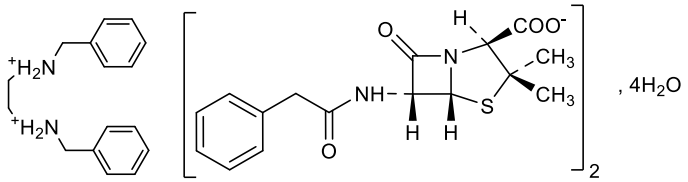
Bendamustine for Injection. Page 1773
Related substances. Impurity table, line 10

Change **from**: Bendamustine related compound G	1.11	----
to: Bendamustine related compound G	0.90	----

Benzathine Penicillin. Page 1778

Para 1

Change **to**:



$C_{16}H_{20}N_2,(C_{16}H_{18}N_2O_4S)_2, 4H_2O$ Mol. Wt. 981.0

Benzathine Penicillin is *N*,*N*'-dibenzylethylenediammonium bis [(6R)-6-(2-phenylacetamido)penicillanate] tetrahydrate.

Benzoic Acid Solution. Page 1788

Insert before **Assay**

Other tests. Comply with the tests stated under Liquids for cutaneous application.

Benzhexol Tablets. Page 1784

Insert before **Other tests**

Uniformity of dosage units (2.5.4). Complies with the test stated under Uniformity of dosage units.

Compound Benzoin Tincture. Page 1789

Insert before **Assay**

Other tests. Comply with the tests stated under Liquids for cutaneous application.

Betamethasone Dipropionate. Page 1810

Insert before **Loss on drying**

Sulphated ash (2.3.18). Not more than 0.2 per cent, using a platinum crucible.

Betamethasone Sodium Phosphate. Page 1814

Identification

Change **to**: **Identification**

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

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

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A freshly prepared mixture of 30 volumes of *isopropyl alcohol*, 10 volumes of *acetic acid* and 10 volumes of *water*.

Test solution. Dissolve 0.25 g of the substance under examination in *water* and dilute to 100.0 ml with *water*.

Reference solution (a). A 0.25 per cent w/v solution of *betamethasone sodium phosphate IPRS* in *water*.

Reference solution (b). A mixture of equal volumes of the test solution and reference solution (a).

Reference solution (c). A mixture of equal volumes of the test solution and a 0.25 per cent w/v solution of *prednisolone sodium phosphate IPRS*.

Apply 2 µl of each solution to the plate. After development, dry the plate in air until the odour of solvents is no longer detectable, spray with *ethanolic sulphuric acid (20 per cent)*, heat at 120° for 10 minutes, allow to cool, and examine in ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution

corresponds to that in the chromatogram obtained with reference solution (a). The principal spot in the chromatogram obtained with reference solution (b) appears as a single, compact spot and the chromatogram obtained with reference solution (c) shows two closely running spots.

C. Dissolve 2 mg in 2 ml of *sulphuric acid* and allow to stand for 5 minutes; no red colour or yellowish-green fluorescence is produced (distinction from prednisolone sodium phosphate and hydrocortisone sodium phosphate).

D. Heat gently 40 mg with 2 ml of *sulphuric acid* until white fumes are evolved, add *nitric acid* dropwise until oxidation is complete and cool. Add 2 ml of *water*, heat until white fumes are again evolved, cool, add 10 ml of *water* and neutralise to *litmus paper* with *dilute ammonia solution*. The solution gives the reactions of sodium salts (2.3.1) and of phosphates (2.3.1).

Betamethasone Sodium Phosphate Tablets. Page 1818

Assay. Insert after chromatographic system
"Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution."

Betamethasone Valerate. Page 1819

Identification
Insert after **Identification**
Tests A and C may be omitted if tests B and D are carried out. Tests B and D may be omitted if tests A and C are carried out.

C.
Change **to**: C. 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 (a).

Assay
After Chromatographic system, line 7
Change **from**: the reference solution
to: reference solution (a)

Betaxolol Eye Drops. Page 1824

Assay. After chromatographic system, para 1
Change **to**: Inject reference solution (b) and (a). The test is not valid unless the resolution between the peaks due to betaxolol and pilocarpine 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 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test Solution.

Bicalutamide. Page 1828

Specific optical rotation. Delete the requirement.

Insert before **Loss on drying**
Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 1.0 g using platinum crucible.

Bumetanide. Page 1880

Para 2
Change **to**: Bumetanide contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{17}H_{20}N_2O_5S$, calculated on the dried basis.

Identification. Change **to**:
Identification

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

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.

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

Solvent mixture. 40 volumes of *methanol* and 60 volumes of *water*.

Test solution. Dissolve 20 mg of the substance under examination in 40 ml of *methanol* and dilute to 100.0 ml with *water*.

Reference solution (a). Dissolve 20 mg of *bumetanide IPRS* in 80 ml of *methanol* and dilute to 200.0 ml with *water*.

Reference solution (b). Dissolve 5 mg of *bumetanide impurity A IPRS* in 20 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (c). Dissolve 5 mg of *bumetanide impurity B IPRS* in 20 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (d). Dissolve 5 mg of *bumetanide impurity C IPRS* in 20 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (e). Dilute 1.0 ml, each of, reference solution (a), reference solution (b), reference solution (c) and reference solution (d) to 10.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution (f). Dilute 1.0 ml, each of, reference solution (a), reference solution (b) and reference solution (c) and reference solution (d) to 20.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 20.0 ml with the solvent mixture. Further dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
– column temperature: 30°,
– mobile phase: A. 0.5 per cent v/v solution of *formic acid* in *water*,
B. *methanol*,
– a gradient programme using the conditions given below,
– flow rate: 1 ml per minute,
– spectrophotometer set at 254 nm,
– injection volume: 50 µl.

Time (in min.)	Mobile phase (per cent v/v)	Mobile phase (per cent v/v)
0	60	40
2	60	40
10	20	80
15	20	80
15.1	60	40
20	60	40

Name	Relative retention time
Bumetanide impurity B[1]	0.3
Bumetanide impurity A[2]	0.7
Bumetanide	1.0
Bumetanide impurity C[3]	1.4

[1]3-amino-4-phenoxy-5-sulphamoylbenzoic acid,
[2]3-nitro-4-phenoxy-5-sulphamoylbenzoic acid,
[3]Butyl 3-(butylamino)-4-phenoxy-5-sulphamoylbenzoate.

Inject reference solution (e) and (f). The test is not valid unless the resolution between the peaks due to bumetanide impurity B and bumetanide impurity A is not less than 20, the relative standard deviation for replicate injections is not more than 5.0 per cent, for each peak in the chromatogram obtained with reference solution (e) and the signal-to-noise ratio is not less than 10, for each peak in the chromatogram obtained with reference solution (f).

Inject reference solution (e) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to bumetanide impurity B and bumetanide impurity C, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.1 per cent), the area of any peak corresponding to bumetanide impurity A is not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (e) (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 (e) (0.10 per cent) and the sum of areas of all the secondary peaks other than bumetanide impurity B, bumetanide impurity A and bumetanide impurity C is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (e) (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 reference solution (e)) (0.05 per cent).

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

Test solution. Dissolve 20 mg of the substance under examination in *methanol* and dilute to 100.0 ml with *methanol*. Dilute 5.0 ml of the solution to 10.0 ml with *water*.

Reference solution. A 0.02 per cent w/v solution of *bumetanide IPRS* in *methanol*. Dilute 5.0 ml of the solution to 10.0 ml with *water*.

Use chromatographic system as described under Related substances with the following modifications.
– injection volume: 10 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 injection is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{17}H_{20}N_2O_5S$.

Storage. Change **to**:
Storage. Store protected from light and moisture, at a temperature not exceeding 30°.

Bumetanide Injection. Page 1881

Para 3
Change **to**: Bumetanide Injection contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of bumetanide, $C_{17}H_{20}N_2O_5S$.

Identification. B, last line

Change **from**: reference solution (a).
to: the reference solution.

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

Solvent mixture. 40 volumes of *methanol* and 60 volumes of *water*.

Test solution. Use the injection, dilute if necessary, with the solvent mixture to obtain a solution containing 0.025 per cent w/v of Bumetanide.

Reference solution (a). Dissolve 25 mg of *bumetanide IPRS* in 80 ml of *methanol* and dilute to 200.0 ml with *water*.

Reference solution (b). Dissolve 6.25 mg of *bumetanide impurity A IPRS* in 80 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (c). Dissolve 6.25 mg of *bumetanide impurity B IPRS* in 80 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (d). Dilute 2.0 ml, each of, reference solution (a) and reference solution (b) in 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (e). Dilute 2.0 ml, each of, reference solution (a), reference solution (b) and reference solution (c) to 100.0 ml with the solvent mixture. Further dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (f). Dilute 5.0 ml of reference solution (d) to 10.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
– column temperature: 30°,
– mobile phase: A. 0.5 per cent v/v solution of *formic acid* in *water*,
B. *methanol*,
– a gradient programme using the conditions given below,
– flow rate: 1 ml per minute,
– spectrophotometer set at 254 nm,
– injection volume: 50 µl.

Time (in min.)	Mobile phase (per cent v/v)	Mobile phase (per cent v/v)
0	60	40
2	60	40
10	20	80
15	20	80
15.1	60	40
20	60	40

Name	Relative retention time
Bumetanide impurity B[1]	0.3
Bumetanide impurity A[2]	0.7
Bumetanide	1.0

[1]3-amino-4-phenoxy-5-sulphamoylbenzoic acid,
[2]3-nitro-4-phenoxy-5-sulphamoylbenzoic acid.

Inject reference solution (d), (e) and (f). The test is not valid unless the resolution between the peaks due to bumetanide impurity B and bumetanide impurity A is not less than 20 in the chromatogram obtained with reference solution (e), the relative standard deviation for replicate injections is not more than 5.0 per cent, for each peaks in the chromatogram obtained with reference solution (d) and the signal-to-noise ratio is not less than 10, for each peaks in the chromatogram obtained with reference solution (f).

Inject reference solution (d) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to bumetanide impurity B is not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.2 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent) and the sum of areas of all the secondary peaks other than bumetanide impurity B is not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.8 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (d)) (0.1 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Transfer a suitable volume of the injection to a suitable volumetric flask, add *methanol* to about 40 percent of the final volume and dilute to volume with *water* to obtain a solution containing 0.01 per cent w/v of bumetanide.

Reference solution. A 0.02 per cent w/v solution of *bumetanide IPRS* in *methanol*. Dilute 5.0 ml of the solution to 10.0 ml with *water*.

Use chromatographic system as described under Related substances with the following modifications.

– injection volume: 10 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 injection is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{17}H_{20}N_2O_5S$ in the injection.

Insert at the end
Storage. Store protected from light, in a single dose or in multi dose containers, preferably of Type 1 glass.

Bumetanide Oral Solution. Page 1882

Para 3
Change **to**: Bumetanide Oral Solution contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of bumetanide, $C_{17}H_{20}N_2O_5S$.

Identification. Change **to**:

Identification

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.

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

Solvent mixture. 40 volumes of *methanol* and 60 volumes of *water*.

Test solution. Dilute a suitable quantity of oral solution in a suitable volumetric flask by adding about 40 per cent of the volume of *methanol*, shake well and dilute to volume with *water* to obtain a solution containing 0.025 per cent w/v of Bumetanide. Centrifuge the solution at least for 10 minutes and use the clear supernatant liquid.

Reference solution (a). Dissolve 25 mg of *bumetanide IPRS* in 80 ml of *methanol* and dilute to 200.0 ml with *water*.

Reference solution (b). Dissolve 6.25 mg of *bumetanide impurity A IPRS* in 80 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (c). Dissolve 6.25 mg of *bumetanide impurity B IPRS* in 80 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (d). Dilute 2.0 ml, each of, reference solution (a), reference solution (b) and reference solution (c) 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 (e). Dilute 2.0 ml, each of, reference solution (a) and reference solution (b) to 100.0 ml with the solvent mixture. Further dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (f). Dilute 5.0 ml reference solution (d) to 10.0 ml with the solvent mixture.

Chromatographic system

– a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
– column temperature: 30°,
– mobile phase: A. 0.5 per cent v/v solution of *formic acid* in *water*,
B. *methanol*,
– a gradient programme using the conditions given below,
– flow rate: 1 ml per minute,
– spectrophotometer set at 254 nm,
– injection volume: 50 µl.

Time (in min.)	Mobile phase (per cent v/v)	Mobile phase (per cent v/v)
0	60	40
2	60	40
10	20	80
15	20	80
15.1	60	40
20	60	40

Name	Relative retention time
Bumetanide impurity B[1]	0.3
Bumetanide impurity A[2]	0.7
Bumetanide	1.0

[1]3-amino-4-phenoxy-5-sulphamoylbenzoic acid,
[2]3-nitro-4-phenoxy-5-sulphamoylbenzoic acid.

Inject reference solution (d), (e) and (f). The test is not valid unless the resolution between the peaks due to bumetanide impurity B and bumetanide impurity A is not less than 20 in the chromatogram obtained with reference solution (e), the relative standard deviation for replicate injections is not more than 5.0 per cent, for each peaks in the chromatogram obtained with reference solution (d) and the signal-to-noise ratio is not less than 10, for each peaks in the chromatogram obtained with reference solution (f).

Inject reference solution (d) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to bumetanide impurity B is not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.2 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent) and the sum of areas of all the secondary peaks other than bumetanide impurity B is not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.8 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (d)) (0.1 per cent).

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

Test solution. Mix a quantity of the oral solution containing 5 mg of Bumetanide with *methanol*, with the aid of ultrasound and dilute to 25.0 ml with *methanol*. Centrifuge for 10 minutes. Dilute 5.0 ml of the supernatant to 10.0 ml with *water*.

Reference solution. A 0.02 per cent w/v solution of *bumetanide IPRS* in *methanol*. Dilute 5.0 ml of the solution to 10.0 ml with *water*.

Use chromatographic system as described under Related substances with the following modifications.
– injection volume: 10 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 injection is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{17}H_{20}N_2O_5S$ in oral solution.

Determine the weight per ml of the oral solution (2.4.29) and calculate the content of $C_{17}H_{20}N_2O_5S$ weight in volume.

Bumetanide Tablets. Page 1883

Para 1

Change **to**: Bumetanide Tablets contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of bumetanide, $C_{17}H_{20}N_2O_5S$.

Identification. B, last line

Change **from**: reference solution (a).

to: the reference solution.

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 40 volumes of *methanol* and 60 volumes of *water*.

Test solution. Transfer a suitable quantity of intact tablets (not less than 10 tablets) to a suitable volumetric flask, add about 40 per cent of the volume of *methanol*, shake well until the tablets are disintegrate and dilute to volume with *water* to obtain a solution containing 0.025 per cent w/v of Bumetanide. Centrifuge the solution at least 10 minutes and use the clear supernatant liquid.

Reference solution (a). Dissolve 25 mg of *bumetanide IPRS* in 80 ml of *methanol* and dilute to 200.0 ml with *water*.

Reference solution (b). Dissolve 6.25 mg of *bumetanide impurity A IPRS* in 80 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (c). Dissolve 6.25 mg of *bumetanide impurity B IPRS* in 80 ml of *methanol* and dilute to 50.0 ml with *water*.

Reference solution (d). Dilute 2.0 ml, each of, reference solution (a) and reference solution (b) 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 (e). Dilute 2.0 ml, each of, reference solution (a), reference solution (b) and reference solution (c) 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 (f). Dilute 5.0 ml reference solution (d) to 100.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
– column temperature: 30°,
– mobile phase: A. 0.5 per cent v/v solution of *formic acid* in *water*,
B. *methanol*,
– a gradient programme using the conditions given below,
– flow rate: 1 ml per minute,
– spectrophotometer set at 254 nm,
– injection volume: 50 µl.

Time (in min.)	Mobile phase (per cent v/v)	Mobile phase (per cent v/v)
0	60	40
2	60	40
10	20	80
15	20	80
15.1	60	40
20	60	40

Name	Relative retention time
Bumetanide impurity B[1]	0.3
Bumetanide impurity A[2]	0.7
Bumetanide	1.0

[1]3-amino-4-phenoxy-5-sulphamoylbenzoic acid,
[2]3-nitro-4-phenoxy-5-sulphamoylbenzoic acid.

Inject reference solution (d), (e) and (f). The test is not valid unless the resolution between the peaks due to bumetanide impurity B and bumetanide impurity A is not less than 20 in the chromatogram obtained with reference solution (e), the relative standard deviation for replicate injections is not more than 5.0 per cent, for each peaks in the chromatogram obtained with reference solution (d) and the signal-to-noise ratio is not less than 10, for each peaks in the chromatogram obtained with reference solution (f).

Inject reference solution (d) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to bumetanide impurity B is not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.2 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent) and the sum of areas of all the secondary peaks other than bumetanide impurity B is not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.8 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (d)) (0.1 per cent).

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

Test solution. Transfer a suitable quantity of intact tablets (not less than 10 tablets) to a suitable volumetric flask, add about 40 per cent of the volume of *methanol*, shake well until the tablets are disintegrate and dilute to volume with *methanol* to obtain 0.02 per cent w/v solution of bumetanide. Centrifuge for 10 minutes. Dilute 5.0 ml of the clear supernatant to 10.0 ml with *water*. (*NOTE-Sonication may be necessary for complete disintegration)*.

Reference solution. A 0.02 per cent w/v solution of *bumetanide IPRS* in *methanol*. Dilute 5.0 ml of the solution to 10.0 ml with *water*.

Use chromatographic system as described under Related substances with the following modifications.
– injection volume: 10 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 injection is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{17}H_{20}N_2O_5S$ in the tablets.

Insert at the end
Storage. Store protected from light and moisture, at a temperature not exceeding 30°.

Buprenorphine Injection. Page 1888

Related substances. *Reference solution (a)*
Change **from**: A 0.00015 per cent w/v solution of *buprenorphine hydrochloride IPRS* in *methanol*.
to: A solution of *buprenorphine hydrochloride IPRS* containing 0.00015 per cent of buprenorphine in *methanol*.

Caffeine. Page 1918

Para 2, line 3 and 4
Change **from**: anhydrous basis
to: dried basis

Loss on drying
Insert at the end

,determined on 1.0 g by drying in an oven at 80˚ for 4 hours.

Calcium Orotate. Page 1932

pH. Insert at the end

(NOTE- Dissolve the substance in boiling water, cool to room temperature before pH determination)

Assay. Line 9
Change **from**: 0.019315 g
to: 0.017515 g

Dibasic Calcium Phosphate, Anhydrous. Page 1933

Identification
Change **from**: Dissolve 0.1 g by warming in 10 ml of *2 M hydrochloric acid*, add drop wise 2.5 ml of *dilute ammonia solution* with shaking, and then add 5 ml of *ammonium oxalate solution*; a white precipitate is formed.

Dissolve 0.1 g in 5 ml of *dilute nitric acid*, heat the solution to 70º, and add 2 ml of freshly prepared 10 per cent w/v solution of *ammonium molybdate*; a yellow precipitate is formed.

to: A. Dissolve 0.1 g by warming in 10 ml of *2 M hydrochloric acid*, add drop wise 2.5 ml of *dilute ammonia solution* with shaking, and then add 5 ml of *ammonium oxalate solution*; a white precipitate is formed.

B. Dissolve 0.1 g in 5 ml of *dilute nitric acid*, heat the solution to 70º, and add 2 ml of freshly prepared 10 per cent w/v solution of *ammonium molybdate*; a yellow precipitate is formed.

Dibasic Calcium Phosphate, Dihydrate. Page 1935

Identification
Change **from**: Dissolve 0.1 g by warming in 10 ml of *2 M hydrochloric acid*, add drop wise 2.5 ml of *dilute ammonia solution* with shaking, and then add 5 ml of *ammonium oxalate solution*; a white precipitate is formed.

Dissolve 0.1 g in 5 ml of *dilute nitric acid*, heat the solution to 70º, and add 2 ml of freshly prepared 10 per cent w/v solution of *ammonium molybdate*; a yellow precipitate is formed.

to: A. Dissolve 0.1 g by warming in 10 ml of *2 M hydrochloric acid*, add drop wise 2.5 ml of *dilute ammonia solution* with shaking, and then add 5 ml of *ammonium oxalate solution*; a white precipitate is formed.

B. Dissolve 0.1 g in 5 ml of *dilute nitric acid*, heat the solution to 70º, and add 2 ml of freshly prepared 10 per cent w/v solution of *ammonium molybdate*; a yellow precipitate is formed.

Carbamazepine. Page 1950

Identification. Insert at the end
C. Melting range (2.4.21). 189° to 193°.

Carisoprodol. Page 1971

Insert before **Loss on drying**
Sulphated ash (2.3.18). Not more than 0.1 per cent.

Cefadroxil. Page 1985

Identification
Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *cefadroxil IPRS* or with the reference spectrum of cefadroxil.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel H* and impregnating the dry plate by placing it in a tank containing a shallow layer of about 1 cm of a mixture of 95 volumes of *n-hexane* and 5 volumes of *1-tetradecane*, allowing the solvent to ascend to the top, removing the plate and allowing the solvent to evaporate.

Mobile phase. A mixture of 60 volumes of *0.1 M citric acid*, 40 volumes of 0.1 M *disodium hydrogen orthophosphate* and 1.5 volumes of 6.66 per cent w/v solution of *ninhydrin* in *acetone*.

Test solution. A 0.2 per cent w/v solution of the substance under examination in *water*.

Reference solution (a). A 0.2 per cent w/v solution of *cefadroxil IPRS* in *water*.

Reference solution (b). A mixture of equal volumes of the test solution and reference solution (a).

Apply to the plate 20 µl of each solution. After development, dry the plate in air, spray with a 0.2 per cent w/v solution of *ninhydrin* in *ethanol*, dry at 110° for 10 minutes and examine. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (a). The principal spot in the chromatogram obtained with reference solution (b) appears as a single compact spot.

Insert before **Water**
Sulphated ash (2.3.18). Not more than 0.1 per cent.

Cefpodoxime for Oral Suspension. Page 2018

Assay. *Reference solution*
Change **to**: *Reference solution.* A solution of *cefpodoxime proxetil IPRS* containing 0.0025 per cent w/v solution of cefpodoxime in the solvent mixture.

Cetrimide Emulsifying Ointment. Page 2058

Para 2
Change **from**: Cetrimide Emulsifying Ointment contains not less than 2.5 per cent and not more than 3.3 per cent w/w of the stated amount of cetrimide, $C_{17}H_{38}BrN$.
to: Cetrimide Emulsifying Ointment contains not less than 85.0 per cent and not more than 110.0 per cent w/w of the stated amount of cetrimide, $C_{17}H_{38}BrN$.

Chlorothiazide Tablets. Page 2091

Assay. Change **to**:

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

Test solution. Weigh and powder 20 Tablets. Disperse a quantity of the powder containing 25 mg of Chlorothiazide in 40 ml of the solvent mixture, with the aid of ultrasound and dilute to 50.0 ml with the solvent mixture, centrifuge. Dilute 2.0 ml of the clear supernatant liquid to 10.0 ml with the solvent mixture.

Reference solution. A 0.01 per cent w/v solution of *chlorothiazide IPRS* in the solvent mixture.

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 injection is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_7H_6ClN_3O_4S_2$ in the tablets.

Chloroxylenol. Page 2092

Assay. Change **to**:

Assay. Weigh accurately about 70 mg, dissolve in 30 ml of *glacial acetic acid*, add 25.0 ml of *0.0167 M potassium bromate*, 20 ml of 15 per cent w/v solution of *potassium bromide* and 10 ml of *hydrochloric acid*, stopper the flask and allow to stand protected from light for 15 minutes. Add 1 g of *potassium iodide* and 100 ml of *water* and titrate with *0.1 M sodium thiosulphate*, shaking vigorously and using 1 ml of *starch solution* as indicator. Repeat the procedure without the substance under examination. The difference between the titrations represents the amount of *potassium bromate* required.

1 ml of *0.0167 M potassium bromate* is equivalent to 0.003915 g of C_8H_9ClO.

Chlorpheniramine Maleate. Page 2093

Related substances. After chromatographic system, para 1, line 5
Change **from**: chlorpheniramine
to: pheniramine

Chlorpromazine Hydrochloride. Page 2096

Identification
Change **from**: *Test A may be omitted if tests B, C and D are carried out. Test B may be omitted if tests A, C and D are carried out.*
to: *Test A may be omitted if tests B, C and D are carried out. Tests B and C may be omitted if tests A and D are carried out.*

Cilastatin Sodium. Page 2111

Insert before **Storage**
Cilastatin Sodium intended for use in the manufacture of parenteral preparations without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Ciprofloxacin Tablets. Page 2131

Assay. *Reference solution (a)*
Change **from**: A 0.02 per cent w/v solution of *ciprofloxacin hydrochloride IPRS* in the solvent mixture.
to: A solution of *ciprofloxacin hydrochloride IPRS* containing 0.02 per cent w/v of ciprofloxacin in the solvent mixture.

Cisplatin Injection. Page 2133

Para 1
Change **from**: Cisplatin Injection is a sterile solution of Cisplatin in water for injections. It is either supplied as a ready-to-use solution or it is prepared by dissolving Cisplatin for Injection in the requisite amount of water for injections immediately before use.
to: Cisplatin Injection is a sterile solution of Cisplatin in water for injections.

Para 2
Change **from**: *The injection complies with the requirements stated under Parenteral Preparations.*
to: *The injection complies with the requirements stated under Parenteral Preparations (Injections).*

Para 3
Delete the requirement.

Clarithromycin. Page 2144

Related substances. Insert after RRT table
NOTE — Not more than four impurities exceed 0.4 per cent.

Last para, lines 7 to 9
Change **from**: Ignore any peak with an area less than 0.2 times of the principal peak obtained with reference solution (b) (0.2 per cent).
to: Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the peaks eluting before impurity I and after impurity H.

Clarithromycin Tablets. Page 2148

Related substances. Insert after RRT table
NOTE — Not more than four impurities exceed 0.4 per cent.

Clindamycin Palmitate Hydrochloride for Oral Solution. Page 2157

Assay. After chromatographic system, line 4
Change **from**: Calculate the content of $C_{18}H_{33}ClN_2O_5S$, in the oral suspension.

to: Determine the weight per ml of the oral suspension (2.4.29) and calculate the content of $C_{18}H_{33}ClN_2O_5S$, weight in volume.

Clobetasol Propionate. Page 2167

Related substances. *Reference solution (c)*, line 1 and 2
Change **from**: Dissolve the contents of a vial of *clobetasol impurity J IPRS*
to: Dissolve 0.4 mg of *clobetasol impurity J IPRS*

Clomipramine Hydrochloride. Page 2176

Assay. Para 1
Insert at the end
Read the volume added between the 2 points of inflection.

Cloxacillin Sodium. Page 2195

Water. Line 1
Change **from**: Not more than 4.5 per cent
to: 3.0 per cent to 4.5 per cent

Cloxacillin for Oral Solution. Page 2198

Insert before **Assay**
Other tests. Comply with the tests stated under Oral Powders.

Codeine Phosphate. Page 2201

Loss on drying. Line 1
Change **from**: Not more than 3.0 per cent
to: 1.5 per cent to 3.0 per cent

Cyproheptadine Hydrochloride. Page 2254

Para 2
Delete the following requirement.
"Cyproheptadine Hydrochloride contains not less than 98.5 per cent and not more than 101.0 per cent of $C_{21}H_{21}N,HCl$, calculated on anhydrous basis."

Related substances. *Reference solution (a)*, line 1
Change **from**: 0.002 per cent
to: 0.0002 per cent

Hard Cellulose Capsule Shells. Page 2045

Arsenic
Change **to**: **Arsenic** (2.3.10). Dissolve 3.3 g of capsule shells in 15 ml of *hydrochloric acid* and dilute to 50.0 ml with *carbon dioxide free water*. The resulting solution complies with the limit test for arsenic (3 ppm) or determined by ICPMS (2.4.42).

Disintegration. Insert at the end
(NOTE — This test is not applicable to the capsules intended to use for inhalation preparations).

Clozapine. Page 2199

Change **to**: **Clozapine**

$C_{18}H_{19}ClN_4$ Mol. Wt. 326.8

Clozapine is 8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine.

Clozapine contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{18}H_{19}ClN_4$, calculated on the dried basis.

Category. Antipsychotic.

Description. A pale yellow to yellow crystalline powder.

Identification

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

B. 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 (a).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 80 volumes of *methanol* and 20 volumes of *water.*

Buffer solution. Dissolve 2 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 2.4 to 2.5 with *orthophosphoric acid*.

Test solution. Dissolve 37.5 mg of the substance under examination in 40 ml of *methanol*, with the aid of ultrasound for 5 minutes and dilute to 50.0 ml with *water*.

Reference solution (a). A 0.0075 per cent w/v solution of *clozapine IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve 4 mg of *clozapine resolution mixture IPRS* in 4 ml of *methanol*, add 1 ml of *water* and dilute to 10.0 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 Inertsil ODS-3),
- mobile phase: A. a mixture of 10 volumes of *acetonitrile*, 10 volumes of *methanol* and 80 volumes of the buffer solution,
  B. a mixture of 40 volumes of *acetonitrile*, 40 volumes of *methanol* and 20 volumes of the buffer solution,
- a gradient programme using the conditions given below,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 257 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
4	100	0
24	0	100
29	0	100
40	100	0
45	100	0

Name	Relative retention time	Correction factor
Demethyl clozapine[1]	0.9	---
Clozapine	1.0	---
Benzoyl methylpiperazine analog[2]	1.1	2.85
Chlorodibenzodiazepinone[3]	1.6	0.83
Didiazepinyl piperazine[4]	1.7	---

[1]8-Chloro-11-(piperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine,

[2]1-[2-[(2-Amino-4-chlorophenyl)amino]benzoyl]-4-methylpiperazine,
[3]8-Chloro-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one,
[4]1,4-Bis(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)piperazine.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to demethyl clozapine and clozapine is not less than 2.5 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 demethyl clozapine 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 benzoyl methylpiperazine analog and didiazepinyl piperazine, each of, is not more than twice 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 chlorodibenzodiazepinone 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 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) and the sum of areas of all the secondary peaks is not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent).

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 in an oven at 105° for 4 hours.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 80 volumes of *methanol* and 20 volumes of *water.*

Test solution. Dissolve 50 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 5.0 ml of the solution to 50.0 ml with the solvent mixture.

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

Reference solution (b). Transfer 10 mg of *clozapine IPRS* to a 100-ml volumetric flask, add 5 ml of *0.1 M hydrochloric acid*, heat for 2 hours at 90°, add 15 ml of *water* and dilute to volume with *methanol*. Dilute 5.0 ml of the solution to 10.0 ml with reference solution (a).

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm) (such as Intersil C8 3V),
- mobile phase: a mixture of 800 volumes of *methanol* and 200 volumes of *water*, add 0.75 volumes of *triethylamine*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 257 nm,
- injection volume: 10 µl.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to clozapine and any other peak is not less than 1.5 in the chromatogram obtained with reference solution (b), 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 the test solution.

Calculate the content of $C_{18}H_{19}ClN_4$.

Storage. Store protected from moisture.

Clozapine Tablets. Page 2200

Identification

Change **to**: **Identification**

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 (a).

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

Solvent mixture. 80 volumes of *methanol* and 20 volumes of *water.*

Buffer solution. Dissolve 2 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 2.4-2.5 with *orthophosphoric acid*.

Test solution. Disperse a quantity of the powdered tablets containing 0.3 g of Clozapine in 80 ml of *methanol* with the aid of ultrasound for 10 minutes and dilute to 100.0 ml with *water*. Dilute 5.0 ml of the solution to 20.0 ml with the solvent mixture. Centrifuge a portion of the solution at 10000 rpm for 10 minutes and use the supernatant.

Reference solution (a). A 0.0075 per cent w/v solution of *clozapine 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 0.75 per cent w/v of *clozapine resolution mixture IPRS* and 0.00075 per cent w/v of *clozapine-N-oxide* in *methanol* (80 per cent of the final volume) and dilute to volume with *water*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). Dilute 5.0 ml of 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 octadecylsilane bonded to porous silica (5 µm) (such as Inertsil ODS-3),
- column temperature: 35°,
- mobile phase: A. a mixture of 10 volumes of *acetonitrile*, 10 volumes of *methanol* and 80 volumes of the buffer solution,
  B. a mixture of 40 volumes of *acetonitrile*, 40 volumes of *methanol* and 20 volumes of the buffer solution,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 257 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
4	100	0
24	0	100
29	0	100
30	100	0
35	100	0

Name	Relative retention time	Correction factor
Demethyl clozapine[1]	0.9	---
Clozapine	1.0	---
Benzoyl methylpiperazine analog[2]	1.10	2.78
Clozapine *N*-oxide[3]	1.13	1.15
Chlorodibenzodiazepinone[4]	1.6	0.83
Didiazepinyl piperazine[5]	1.7	---

[1]8-Chloro-11-(piperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine,
[2]1-[2-[(2-Amino-4-chlorophenyl)amino]benzoyl]-4-methylpiperazine,
[3]4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylpiperazine 1-oxide.
[4]8-Chloro-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one,
[5]1,4-Bis(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)piperazine.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to benzoyl methylpiperazine analog and clozapine *N*-oxide and between chlorodibenzodiazepinone and didiazepinyl

piperazine 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) 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 test solution, the area of any peak corresponding to demethyl clozapine 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 benzoyl methylpiperazine analog, clozapine *N*-oxide and chlorodibenzodiazepinone, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than twice 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 20 times the area of the principal peak in the chromatogram obtained with reference solution (a) (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 (a) (0.1 per cent).

Dapagliflozin and Metformin Hydrochloride Prolonged-release Tablets. Page 2284

Dissolution. Change **to**:
Dissolution. (2.5.2).

For Dapagliflozin —

Apparatus No. 1 (Basket),
Medium. 1000 ml of phosphate buffer pH 6.8, prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 0.9 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution*.
Speed and time. 100 rpm and 20 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Use the filtrate, dilute if necessary, with the dissolution medium.

Reference solution. Weight and transfer 25 mg of *dapagliflozin IPRS* to a 100-ml volumetric flask, add 10 ml of *acetonitrile*, sonicate for 5 minutes to dissolve and dilute to volume with the dissolution medium. Dilute 2.0 ml of the solution to 100.0 ml with the dissolution medium.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Kromasil C18),
- column temperature: 30º,
- sample temperature: 25°,
- mobile phase: a mixture of 65 volumes of a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 2.0 with *dilute orthophosphoric acid* and 35 volumes of *acetonitrile,*
- flow rate: 1.4 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 50 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 4000 theoretical plates, the tailing factor is not more than 1.5 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 $C_{21}H_{25}ClO_6$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{21}H_{25}ClO_6$.

For Metformin Hydrochloride — Complies with the test stated under Tablets.

Dasatinib. Page 2303

Related Substances. After Impurity Table, IUPAC names
Change **to**:
[1] 2-Amino-N-(2-chloro-6-methylpheyl)-thiozole-5-carbomide,
[2] N-(2-chloro-6-methylpheyl)-2-[[6-chloro-2-methyl-4-pyrimidinyl] amino]-5thiazolecarboxamide.

Daunorubicin for Injection. Page 2307

Insert at the end
Labelling. The label states the strength in terms of the equivalent amount of daunorubicin.

Dextrose. Page 2355

Identification. A
Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *dextrose IPRS* or with the reference spectrum of dextrose (*Note- Dry the substance under vacuum at 70° for 2 hours for dextrose monohydrate*).

Dicloxacillin Capsules. Page 2376

Insert at the end
Labelling. The label states the strength in terms of the equivalent amount of Dicloxacillin.

Dicloxacillin for Oral Suspension. Page 2377

Other tests
Change **from**: Oral Liquids.
to: Oral Powders.

Ferric Carboxymaltose. Page 2655

Zeta potential. Line 1
Change **from**: Limit not less than +3.0.
to: Limit not less than +3.0 (mV).

Fexofenadine Hydrochloride. Page 2663

Chlorides. Line 1
Insert at the end
,calculated on anhydrous basis.

Finasteride. Page 2671

Related substances. After RRT table, line 2
Change **from**: carboxamide (Δ-1,5-aza amide)
to: (dihydrofinasteride)

Line 4
Change **from**: (dihydrofinasteride)
to: carboxamide (Δ5-finasteride)

Fructose. Page. 2750

Change **to**: **Fructose**

D-Fructose

$C_6H_{12}O_6$ Mol. Wt. 180.2

Fructose is D-(-)-fructopyranose.

Fructose contains not less than 98.0 per cent and not more than 102.0 per cent of $C_6H_{12}O_6$, calculated on dried basis.

Category. Nutrient; fluid replenisher.

Description. A white or colourless crystalline powder with a very sweet taste.

Identification

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

Tests

Appearance of solution. Dissolve 5.0 g in *water* and dilute to 10 ml with *water*. The solution is clear (2.4.1). Add 10 ml of *water*. The solution is colourless (2.4.1).

Acidity. Dissolve 5.0 g in 50 ml of *carbon dioxide-free water* and add *phenolphthalein solution*. Not more than 0.50 ml of *0.02 M sodium hydroxide* is required to change the colour of the solution to pink.

5-Hydroxymethylfurfural and related compounds. To 5 ml of 10 per cent w/v solution, add 5 ml of *water* and measure the absorbance of the resulting solution at the maximum at about 284 nm (2.4.7) is not more than 0.32.

Chlorides (2.3.12). 1.38 g complies with the limit test for chlorides (180 ppm).

Sulphates (2.3.17). 0.6 g complies with the limit test for sulphates (250 ppm).

Calcium and Magnesium (as Calcium). Not more than 0.005 per cent.

Weigh 20 g and dissolve in 200 ml of *water.* Add 2 drops of *hydrochloric acid*, 5 ml of *ammonia-ammonium chloride buffer* and 8 drops of *eriochrome black T* indicator, mix. Titrate with *0.005 M disodium edetate* until a blue colour is obtained. Not more than 5.0 ml of *0.005 M disodium edetate* is consumed.

1 ml of *0.005 M disodium edetate* is equivalent to 0.0002004 g of calcium.

Sulphated ash (2.3.18). Not more than 0.5 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, by drying under vaccum at 70° for 4 hours.

Fructose intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Not more than 0.5 Endotoxin Unit per ml of a 5 per cent w/v solution in Water for Injections.

Assay. Weigh 10 g of substances under examination previously dried under vacuum at 70° for 4 hours and transfer to a 100-ml volumetric flask, dissolve in 50 ml of *water*. Add 0.2 ml of *6 M ammonium hydroxide* and dilute to volume with *water*. Mix well, allow to stand for 30 minutes and determine the optical rotation (2.4.22), using 100 mm tube length.

Calculate the percentage of fructose, $C_6H_{12}O_6$ using following expression:

$$\text{Fructose, } C_6H_{12}O_6 \text{ (per cent)} = \frac{a \times F}{W} \times 100$$

Where,
a = observed rotation (°)
F = correction factor, -1.124
W = weight of substance under examination (g)

Storage. Store protected from moisture.

Labelling. The label states whether or not the contents are intended for use in the manufacture of parenteral preparations.

Fructose Injection. Page 2751

Assay. Change **to**:

Assay. To a measured volume containing about 5 g of Fructose, add 0.2 ml of *6 M ammonium hydroxide* and dilute to 100.0 ml with *water*. Mix well, allow to stand for 30 minutes and determine the optical rotation (2.4.22).

Calculate the percentage of fructose, $C_6H_{12}O_6$ using following expression:

Fructose, $C_6H_{12}O_6$ (per cent) = $[(F \times \alpha)/(l \times V \times L)] \times 100$

Where,
F = correction factor, 1124,
α = observed angle of rotation as an absolute number,
l = length of the polarimeter tube (dm),
V = volume of injection taken (ml)
L = labeled amount of fructose in Injection (mg/ml)

Frusemide. Page 2752

Assay. After chromatographic system, para 1, line 3
Change **from**: 2.5
to: 1.5

Fulvestrant. Page 2756

Enantiomeric purity. Line 1 and 2
Change **from**: Fulvestrant epimer B is 52.0 to 58.0 per cent and Fulvestrant epimer A is 42.0 to 48.0 per cent.
to: Fulvestrant epimer B is 52 to 58 per cent and Fulvestrant epimer A is 42 to 48 per cent.

Gelatin. Page 2779

Peroxides. Lines 3 to 7
Change **from**: Remove the test strip, shake off excess liquid and compare the reaction zone after 15 seconds with the colour scale provided with the test strips used. The colour must match that of the 10 ppm concentration, otherwise the test is invalid.
to: Remove the test strip, shake off excess liquid and after 15 seconds, compare the reaction zone with the colour scale provided. The test strips are suitable if the colour matches that of the 2 ppm concentration.

Hydrochlorothiazide. Page 2858

Assay. *Test solution*, line 1
Change **from**: *Test solution.*
to: *Test solution (a).*

Reference solution, line 1
Change **from**: *Reference solution.*
to: *Reference solution (c).*

After impurity table, line 1
Change **from**: the reference solution
to: reference solution (a)

Line 4
Change **from**: Inject the reference solution and the test solution.
to: Inject reference solution (c) and test solution (a).

Hydrocortisone Sodium Succinate for Injection. Page 2869

Related substances. *Reference solution (b)*

Change **to**: *Reference solution (b)*. A 0.035 per cent w/v solution of *hydrocortisone IPRS* in *acetonitrile*. Dilute 5.0 ml of the solution to 10.0 ml with *water*.

Hydroxyethyl Cellulose. Page 2877

Nitrates. Para 1, line 2 and 5
Change **from**: 100 mPa.s
to: 1000 mPa.s

Hyoscine Butylbromide. Page 2892

Related substances. *Reference solution (a)*, line 2
Change **from**: the mobile phase.
to: mobile phase B.

Levetiracetam Prolonged-release Tablets. Page 3089

Related substances, RRT table
Change **to**:

Name	Relative retention time
Levetiracetam impurity B[1*]	0.40
Levetiracetam	1.0
Levetiracetam acid[2]	1.3
Levetiracetam impurity A[3*]	1.9

*Process impurity included for identification only, not to be included in total degradation product.
[1](*S*)-2-aminobutanamide,
[2](*S*)-2-(2-oxopyrrolidin-1-yl)butanoic acid,
[3](*S*)-*N*-(1-amino-1-oxobutan-2-yl)-4-chlorobutanamide.

Levetiracetam Tablets. Page 3090

Related substances, RRT table
Change **to**:

Name	Relative retention time	Correction factor
Levetiracetam impurity B[1*]	0.54	---
Levetiracetam	1.0	---
Levetiracetam impurity A[2*]	1.7	---
Levetiracetam acid[3]	2.1	1.27

*Process impurity included for identification only, not to be included in total degradation product.
[1](*S*)-2-aminobutanamide hydrochloride,
[2](*S*)-*N*-(1-amino-1-oxobutan-2-yl)-4-chlorobutanamide,
[3](*S*)-2-(2-oxopyrrolidine-1-yl)butanoic acid.

Levonorgestrel. Page 3108

Related substances. Change **to**:
Related substances
A. Levonorgestrel Impurities A, B, H, K, M, O, S, U. Determine by liquid chromatography (2.4.14).

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

Test solution. Dissolve 10 mg of the substance under examination in 7 ml of *acetonitrile* with the aid of ultrasound and dilute to 10.0 ml with *water*.

Reference solution (a). A 0.0001 per cent w/v solution of *levonorgestrel IPRS* in the solvent mixture.

Reference solution (b). Dissolve 5 mg of *levonorgestrel for system suitability 1 IPRS* (containing levonorgestrel impurities A, H, K, M, O and S) in 3.5 ml of *acetonitrile* with the aid of ultrasound and dilute to 5.0 ml with *water*.

Reference solution (c). Dissolve 5.0 mg of *levonorgestrel impurity B IPRS* in 35 ml of *acetonitrile* and dilute to 50.0 ml with *water*. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (d). Dissolve 5.0 mg of *norethisterone IPRS* (levonorgestrel impurity U) in 35 ml of *acetonitrile* and dilute to 50.0 ml with *water*. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octylsilane bonded to porous silica (5 µm),
- column temperature: 30°,
- mobile phase: A. a mixture of 40 volumes of *acetonitrile* and 60 volumes of *water*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 0.7 ml per minute,
- spectrophotometer set at 215 nm and for impurity O at 200 nm,
- injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
50	20	80
51	100	0
55	100	0

Name	Relative retention time	Correction factor
Levonorgestrel impurity H[1]	0.5	---
Levonorgestrel impurity U[2]	0.8	---
Levonorgestrel impurity K[3]	0.85	---
Levonorgestrel impurity A[4]	0.91	0.4
Levonorgestrel impurity M[5]	0.95	3.1
Levonorgestrel (Retention time: about 20 minutes)	1.0	---
Levonorgestrel impurity O[6]	1.16	2.6
Levonorgestrel impurity B[7]	1.26	---
Levonorgestrel impurity S[8]	1.9	---

[1]13-ethyl-6β,17-dihydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (6β-hydroxylevonorgestrel),
[2]17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one (norethisterone),
[3]13-ethyl-17β-hydroxygon-4-en-3-one (18-methylnandrolone),
[4]13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,8(14)-dien-20-yn-3-one,
[5]13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,6-dien-20-yn-3-one (Δ6-levonorgestrel),
[6]13-ethyl-17-hydroxy-5α-methoxy-18,19-dinor-17α-pregn-20-yn-3-one (4,5-dihydro-5α-methoxylevonorgestrel),
[7]13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-5(10)-en-20-yn-3-one,
[8]13-ethyl-3-methoxy-18,19-dinor-17α-pregna-3,5-dien-20-yn-17-ol.

Inject reference solution (b) at 215 nm to identify the peaks due to levonorgestrel impurity A, H, K, M and S and at 200 nm to identify the peak due to levonorgestrel impurity O.

Inject reference solution (c) and (d) to identify the peaks due to levonorgestrel impurity B and peaks due to levonorgestrel impurity U, respectively.

Inject reference solution (a) and (b). The test is not valid unless the peak-to-valley ratio is not less than 3.0, where Hp is the height above the baseline of the peak due to levonorgestrel impurity M and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to levonorgestrel impurity A in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio is not less than 60 for the principal peak in the chromatogram obtained with reference solution (a).

Inject reference solutions (a), (c), (d) and the test solution. In the chromatogram obtained with the test solution the area of any peak corresponding to levonorgestrel impurity A and levonorgestrel impurity K, each of, 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 levonorgestrel impurity M and levonorgestrel impurity S, each of, is not more than twice 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 levonorgestrel impurity H 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 peak corresponding to levonorgestrel impurity B is not more than 3 times the area of the principal peak in the

chromatogram obtained with reference solution (c) (0.3 per cent), the area of any peak corresponding to levonorgestrel impurity U is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent), the area of any peak corresponding to levonorgestrel impurity O at 200 nm 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 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), the sum of the areas of all the secondary peaks other than levonorgestrel impurity O is not more than 10 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 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

B. Levonorgestrel Impurities V and W. Determine by liquid chromatography (2.4.14).

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

Test solution. Dissolve 10 mg of the substance under examination in 7 ml of *acetonitrile* with the aid of ultrasound and dilute to 10.0 ml with *water*.

Reference solution (a). Dissolve 5.0 mg of *ethinylestradiol IPRS* in 35 ml of *acetonitrile* with the aid of ultrasound and dilute to 50.0 ml with *water*. Dilute 3.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve 5 mg of *levonorgestrel for system suitability 2 IPRS* (containing impurities V and W) in 3.5 ml of *acetonitrile* with the aid of ultrasound and dilute to 5.0 ml with *water*.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (3 µm),
- mobile phase: A. a mixture of 40 volumes of *acetonitrile* and 60 volumes of *water*,
  B. a mixture of 10 volumes of *water* and 90 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 200 nm,
- injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	92	8
1	92	8
3	82	18
6	82	18
16	60	40
21	0	100
32	0	100
33	92	8
40	92	8

Name	Relative retention time
Levonorgestrel impurity W[1]	0.9
Levonorgestrel (Retention time: about 12 minutes)	1.0
Levonorgestrel impurity V[2]	1.9

[1]13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-5,7,9-trien-20-yn-3-one,
[2]13-ethyl-3-methoxy-18,19-dinor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol.

Inject reference solution (b) to identify the peaks due to levonorgestrel impurity V and W.

Inject reference solution (b). The test is not valid unless the resolution between levonorgestrel impurity W and levonorgestrel peaks is not less than 2.8.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution the area of any peak corresponding to levonorgestrel impurity W is not more than 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

levonorgestrel impurity V is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent).

Methylergometrine Maleate. Page 3273

Para 2, line 1 and 2

Change **from**: 95.0 per cent and not more than 105.0 per cent

to: 97.0 per cent and not more than 103.0 per cent

Identification. Change **to**:

Identification

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

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

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

NOTE – Protect the solutions from light throughout the test.

Solvent mixture. Transfer a suitable quantity of *tartaric acid* to a suitable volumetric flask, add *water* (50 per cent of the final volume) and mix, dilute to volume with *methanol* to obtain a solution containing 0.25 per cent w/v of tartaric acid. Allow the mixture to cool before use.

Test solution. Dissolve 20 mg of the substance under examination in the solvent mixture with the aid of mechanical shaker for 15 minutes or until completely dissolved and dilute to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution. A 0.01 per cent w/v solution of *methylergometrine maleate IPRS* in the solvent mixture. *(NOTE-Shake by mechanical means for 15 minutes or until completely dissolved).* Dilute 1.0 ml of the solution to 25.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octylsilane bonded to porous silica (5 µm) (such as Zorbax RX-C8),
- column temperature: 30°,
- mobile phase: a mixture of 20 volumes of *acetonitrile* and 80 volumes of 0.2 per cent w/v solution of *potassium dihydrogen orthophosphate*,
- flow rate: 2 ml per minute,
- fluorescence detector with excitation at 315 nm and emission at 423 nm,
- injection volume: 20 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 injection is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{25}N_3O_2,C_4H_4O_4$.

Storage. Change **to**:

Storage. Store protected from light and moisture, at a temperature between 2° to 8°.

Methylergometrine Injection. Page 3274

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

NOTE – Protect the solutions from light throughout the test.

Solvent mixture. A 0.5 per cent w/v solution of *tartaric acid* in equal volumes of *water* and *methanol*. Allow the mixture to cool before use. *(NOTE - Dissolve tartaric acid with water, then add an equal volume of methanol)*.

Test solution. Dilute a volume of the injection with the solvent mixture to obtain a solution 0.01 per cent w/v of Methylergometrine Maleate.

Reference solution. A 0.01 per cent w/v solution of *methylergometrine maleate IPRS* in the solvent mixture. *(NOTE-Shake by mechanical means for 15 minutes or until completely dissolved).*

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with end-capped octylsilane bonded to porous silica (5 µm) (such as Nucleosil C18),
- column temperature: 30°,
- mobile phase: a mixture of 20 volumes of *acetonitrile* and 80 volumes of *0.015 M potassium dihydrogen orthophosphate*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 20 µl.

Inject the reference solution. 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 injection is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{25}N_3O_2,C_4H_4O_4$ in the injection.

Storage. Change **to**:
Storage. Store protected from light and in single-dose container, preferably of Type I glass. Store in a refrigerator.

Methylergometrine Tablets. Page 3275

Insert before **Related substances**
Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 900 ml of 0.5 per cent w/v solution of *tartaric acid*,
Speed and time. 75 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter. Measure the fluorescence of the solution (2.4.5), suitably diluted with the medium, if necessary, using an excitation wavelength of about 327 nm and an emission wavelength of about 428 nm. Calculate the content of $C_{20}H_{25}N_3O_2,C_4H_4O_4$ in the medium from the fluorescence intensity obtained from a solution of known concentration of *methylergometrine IPRS* in the dissolution medium.

Q. Not less than 70 per cent of the stated amount of methylergometrine, $C_{20}H_{25}N_3O_2,C_4H_4O_4$.

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

NOTE – Protect the solutions from light throughout the test.

Solvent mixture. Transfer a suitable quantity of *tartaric acid* to a suitable volumetric flask, add *water* (50 per cent of the final volume) and mix, dilute to volume with *methanol* to obtain a solution containing 0.25 per cent w/v of tartaric acid. Allow the mixture to cool before use.

Test solution. Transfer 10 intact tablets in 1000-ml volumetric flask, disperse in about 400 ml of the solvent mixture with the aid of mechanical shaker for 15 minutes or until completely disintegrated and dilute to volume with the solvent mixture. Allow the solution to settle for not less than 30 minutes before use and then filter.

Reference solution. A 0.0125 per cent w/v solution of *methylergometrine maleate IPRS* in the solvent mixture. *(NOTE-Shake by mechanical means for 15 minutes or until completely dissolved).* Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octylsilane bonded to porous silica (5 µm) (such as Zorbax RX-C8),

- column temperature: 30°,
- mobile phase: a mixture of 20 volumes of *acetonitrile* and 80 volumes of 0.2 per cent w/v solution of *potassium dihydrogen orthophosphate*,
- flow rate: 2 ml per minute,
- fluorescence detector with excitation at 315 nm and emission at 423 nm,
- injection volume: 10 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 injection is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{25}N_3O_2,C_4H_4O_4$ in the tablets.

Minocycline Hydrochloride. Page 3334

Related substances. *Buffer solution*, line 2
Change **from**: 0.28 per cent
to: 2.8 per cent

Minocycline Capsules. Page 3336

Related substances. *Buffer solution*, line 2
Change **from**: 0.28 per cent
to: 2.8 per cent

Minocycline Tablets. Page 3338

Related substances. *Buffer solution*, line 2
Change **from**: 0.28 per cent
to: 2.8 per cent

Minoxidil. Page 3340

Change **to**: **Minoxidil**

$C_9H_{15}N_5O$ Mol. Wt. 209.3

Minoxidil is 2,4-diamino-6-piperidinopyrimidine 3-oxide.

Minoxidil contains not less than 97.0 per cent and not more than 103.0 per cent of $C_9H_{15}N_5O$, calculated on the dried basis.

Category. Antihypertensive.

Description. A white to off-white, crystalline powder.

Identification

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

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

Related substances. Determine by liquid chromatography (2.4.14).

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

Test solution. Dissolve 25 mg of the substance under examination in 60 ml of the solvent mixture, with the aid of mechanical shaker for 20 minutes and dilute to 100.0 ml with the solvent mixture.

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

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 200.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (4 µm) (such as Nova-Pak C18),
- mobile phase: a 0.2 per cent w/v solution of *sodium lauryl sulphate* in a mixture of 60 volumes of *methanol*, 40 volumes of *water* and 1 volume of *glacial acetic acid*, adjusted to pH 3.0 with *perchloric acid*,
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 40 µl.

Name	Relative retention time	Correction factor
Pyrimidine oxide analog[1]	0.19	2.86
Pyrimidine analog[2]	0.37	2.04
Minoxidil	1.0	---
Deoxyminoxidil[3]	1.45	0.76

[1]4-Chloropyrimidine-2,6-diamine-1-oxide,
[2]6-Chloropyrimidine-2,4-diamine,
[3]6-(Piperidin-1-yl)pyrimidine-2,4-diamine.

Inject reference solution (a) and (b). The test is not valid unless the tailing factor is not more than 2.0, the relative standard deviation for replicate injections is not more than 2.0 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. Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to pyrimidine oxide analog, pyrimidine analog and deoxyminoxidil, each of, is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than 0.05 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 0.5 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 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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 by drying at 50° for 3 hours under vacuum at a pressure not exceeding 5 mm of mercury.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 25 mg of the substance under examination in the mobile phase with the aid of mechanical shaker and dilute to 100.0 ml with the mobile phase.

Reference solution. A 0.025 per cent w/v solution of *minoxidil IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Nucleosil C18),
- mobile phase: a 0.3 per cent w/v solution of *docusate sodium* in a mixture of 70 volumes of *methanol*, 30 volumes of *water* and 1 volume of *glacial acetic acid*, adjusted to pH 3.0 with *perchloric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 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 1.1 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_9H_{15}N_5O$.

Storage. Store protected from light and moisture.

Minoxidil Tablets. Page 3341
Change **to**: **Minoxidil Tablets**

Minoxidil Tablets contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of minoxidil, $C_9H_{15}N_5O$.

Usual strengths. 2.5 mg; 5 mg; 10 mg.

Identification
A. Transfer a portion of the finely powdered tablets containing 10 mg of Minoxidil to a separator, add 25 ml of *water,* and extract with three quantities, each of 15 ml, of *chloroform.* Combine the chloroform extracts and evaporate with the aid of stream of nitrogen. Wash the inside of the container with about 5 ml of *ethanol (95 per cent),* add 0.3 g of *potassium bromide IR* and evaporate under vacuum at 50° until dry. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *minoxidil IPRS* or with the reference spectrum of minoxidil.

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
Dissolution (2.5.2).
Apparatus No. 1 (Basket),
Medium. 900 ml of *phosphate buffer pH 7.2,*
Speed and time. 75 rpm and 15 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtered solution, suitably diluted with the medium if necessary, at the maximum at about 231 nm (2.4.7) for tablets containing up to 10 mg Minoxidil; for tablets containing more than 10 mg of Minoxidil, the wavelength used at about 287 nm. Calculate the content of $C_9H_{15}N_5O$ in the medium from the absorbance obtained from a solution of known concentration of *minoxidil IPRS* in the dissolution medium.

Q. Not less than 75 per cent of the stated amount of $C_9H_{15}N_5O$.

Related substances. Determine by liquid chromatography (2.4.14).

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

Test solution. Disperse a quantity of the powdered tablets containing 25 mg of Minoxidil in 60 ml of the solvent mixture with the aid of mechanical shaker for 20 minutes and dilute to 100.0 ml with the solvent mixture, filter.

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

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (5 µm)
- mobile phase: a 0.2 per cent w/v solution of *sodium lauryl sulphate* in a mixture of 60 volumes of *methanol*, 40 volumes of *water* and 1 volume of *glacial acetic acid*, adjusted to pH 3.0 with *perchloric acid*,
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 40 µl.

Name	Relative retention time
Pyrimidine oxide analog[1*]	0.19
Pyrimidine analog[2*]	0.37

Minoxidil	1.0
Deoxyminoxidil[3*]	1.45

[*] Process-related impurities that are controlled in the drug substance.
[1]4-Chloropyrimidine-2,6-diamine-1-oxide,
[2]6-Chloropyrimidine-2,4-diamine,
[3]6-(Piperidin-1-yl)pyrimidine-2,4-diamine.

Inject reference solution (a) and (b). The test is not valid unless the tailing factor is not more than 2.0, the relative standard deviation for replicate injections is not more than 2.0 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. Run the chromatogram 3 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 0.1 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 including process related impurities is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Uniformity of dosage units (2.5.4). Complies with the tests stated under Uniformity of dosage units.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 5 mg of Minoxidil in the mobile phase with the aid of mechanical shaker for 5 minutes and dilute to 20.0 ml with the mobile phase, filter.

Reference solution. A 0.025 per cent w/v solution of *minoxidil IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as MicroBondapak C18),
- mobile phase: a 0.3 per cent w/v solution of *docusate sodium* in a mixture of 70 volumes of *methanol*, 30 volumes of *water* and 1 volume of *glacial acetic acid*, adjusted to pH 3.0 with *perchloric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 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 $C_9H_{15}N_5O$ in the tablets.

Storage. Store protected from light and moisture, at a temperature not exceeding 30º.

Neotame. Page 3453

Related substances. Last para, line 2 to 6
Change **from**: In the chromatogram obtained with the test solution, the area of peak corresponding to neotame impurity A is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent)

to: In the chromatogram obtained with the test solution, the area of peak corresponding to neotame impurity A is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent)

Montelukast Sodium. Page 3358

Related substances. After RRT table, para 2, line 2
Change **from**: montelukast impurity B

to: montelukast impurity G

Nifedipine. Page 3471

Related substances. After chromatographic system, para 2, line 1 to 3

Change **from**: The test is not valid unless the resolution between the peaks due to the nitrosophenylpyridine analogue and nifedipine is not less than 1.5,

to: The test is not valid unless the resolution between the peaks due to the nitrophenylpyridine analogue and nitrosophenylpyridine analogue is not less than 1.5,

Nitrofurantoin. Page 3484

Para 2, line 3

Change **from**: anhydrous basis.

to: dried basis.

Water. Change **to**:

Loss on drying (2.4.19). Not more than 1.0 per cent for anhydrous form and 6.5 per cent to 7.5 per cent for hydrous form, determined on 1.0 g by drying in an oven at 140° for 30 minutes.

Paracetamol. Page 3616

Related substances. *Reference solution (a),* line 1

Change **from**: 0.0002 per cent

to: 0.002 per cent

Phenytoin Tablets. Page 3705

Insert before **Related substances**

Dissolution (2.5.2).

Apparatus No. 2 (Paddle),

Medium. 900 ml of 0.05 M tris buffer pH 9.0 prepared by dissolving 6.05 g *tris(hydroxymethyl)aminomethane* in 900 ml of *water*, adjust to pH 9.0 with *orthophosphoric acid* and dilute to 1000 ml with *water*, containing 1 per cent w/v solution of *sodium lauryl sulphate*,

Speed and time. 100 rpm and 120 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Use the filtrate, dilute if necessary, with the dissolution medium.

Reference solution. A 0.11 per cent w/v solution of *phenytoin sodium IPRS* in *methanol*. Dilute 5.0 ml of the solution to 100.0 ml with the dissolution medium.

Chromatographic system

- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as YMC-Pack ODS-AM),
- mobile phase: a mixture of 40 volumes of a buffer solution prepared by dissolving 2.722 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.5 with *orthophosphoric acid* and 60 volumes of *methanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 229 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 1500 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.

Inject the reference solution and the test solution.

Calculate the content of $C_{15}H_{11}N_2NaO_2$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_{15}H_{11}N_2NaO_2$.

Assay. Chromatographic system, line 4 to 7
Change **to**: – mobile phase: a mixture of 27 volumes of *methanol*, 23 volumes of *acetonitrile*, 50 volumes of *water*, 0.5 volumes of solution A and 0.1 volume of *glacial acetic acid*,

Pralidoxime Chloride. Page 3766
Change **to**: **Pralidoxime Chloride**

$C_7H_9ClN_2O$ Mol. Wt. 172.6

Pralidoxime Chloride is Pyridinium, 2-[(hydroxyimino)methyl]-1-methyl-, chloride (*E*).

Pralidoxime Chloride contains not less than 97.0 per cent and not more than 102.0 per cent of $C_7H_9ClN_2O$, calculated on the dried basis.

Category. Antidote for cholinesterase inhibitors.

Description. A white to pale-yellow, crystalline powder.

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

B. 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 (b).

C. It gives the reactions of chlorides (2.3.1).

Tests

Chloride content. 20.2 to 20.8 per cent, calculated on the dried basis, determined by the following method.

Dissolve 0.3 g in about 150 ml of *water*, add 20 ml of *glacial acetic acid* and 10 drops of *(4-tert-octylphenoxy)nonaethoxyethanol* and titrate with *0.1 M silver nitrate*, determining the end point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M silver nitrate* is equivalent to 0.003545 g of Cl.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 17 volumes of *acetonitrile* and 83 volumes of *water.*

Test solution. Dissolve 125 mg of the substance under examination in *water*, with the aid of ultrasound and dilute to 100.0 ml with *water*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.125 per cent w/v solution of *pralidoxime chloride IPRS* in *water*. Use sonication to dissolve, if necessary. *(NOTE- Pralidoxime chloride IPRS contains pralidoxime anti-isomer as a minor component.)*

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

Reference solution (c). Dilute 1.0 ml of reference solution (b) 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 (d). Dilute 5.0 ml of reference solution (c) to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm) (such as Zorbax 300 SB-C18),

- mobile phase: a mixture of 83 volumes of a buffer solution prepared by dissolving 1.87 g of *sodium octanesulphonate monohydrate* and 330 mg of *tetraethylammonium chloride* in 1000 ml of *water*, adjusted to pH 4.3 with *0.01 M hydrochloric acid* and 17 volumes of *acetonitrile*,
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 10 µl.

Name	Relative retention time	Correction factor
Pyridine-2-aldoxime	0.7	---
Pralidoxime anti-isomer[1]	0.9	
Pralidoxime	1.0	---

[1] *(Z)*-2-[(Hydroxyimino)methyl]-1-methylpyridin-1-ium chloride.

Inject reference solution (b), (c) and (d). The test is not valid unless the resolution between the peaks due to pralidoxime anti-isomer and pralidoxime is not less than 2.0 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 (c) and the signal-to-noise ratio 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 pyridine-2-aldoxime is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent), the area of any peak corresponding to pralidoxime anti-isomer is not more than 20 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 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 (c) (0.10 per cent) and the sum of areas of all the secondary peaks is not more than 30 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 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 (c) (0.05 per cent).

Sulphated ash (2.3.18). Not more than 0.5 per cent.

Loss on drying (2.4.19). Not more than 2.0 per cent, determined on 1.0 g by drying in an oven at 105° for 3 hours.

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

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to pralidoxime anti-isomer and pralidoxime is not less than 2.0, 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 for pralidoxime chloride peak.

Inject reference solution (b) and the test solution.

Calculate the content of $C_7H_9ClN_2O$.

Pralidoxime Chloride intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Not more than 0.10 Endotoxin Units per mg of pralidoxime chloride.

Pralidoxime Chloride intended for use in the manufacture of parenteral preparations without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from moisture.

Labelling. Label states whether or not the contents are intended for use in the manufacture of parenteral preparations.

Pralidoxime Chloride for Injection. Page 3767
Change **to**: **Pralidoxime Chloride for Injection**

Pralidoxime Chloride for Injection is a sterile material consisting of Pralidoxime Chloride with or without buffering agents and other excipients. It is supplied in a sealed container.

The injection is constituted by dissolving the contents of the sealed container in the requisite amount of sterile water for injections, immediately before use.

The constituted solution complies with the requirements for Clarity of solution and Particulate matter stated under Parenteral Preparations (Powders for injection).

Storage. The constituted solution should be used immediately after preparation but, in any case, within the period recommended by the manufacturer.

Pralidoxime Chloride for Injection contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of pralidoxime chloride, $C_7H_9ClN_2O$.

Usual strength. 1 g.

The contents of the sealed container comply with the requirements stated under Parenteral Preparations (Powders for injection) and with the following requirements.

Identification

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

B. 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 (b).

C. It gives the reactions of chlorides (2.3.1).

Tests

pH (2.4.24). 3.5 to 4.5, determined in a 5.0 per cent w/v solution.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 17 volumes of *acetonitrile* and 83 volumes of *water.*

Test solution. Reconstitute 1 container with 20.0 ml of *water*. Reconstitute 4 more containers. Combine all the solutions in a 500-ml volumetric flask. Rinse each container with water and add the rinsings to the volumetric flask and dilute to volume with *water*. Dilute 25.0 ml of the pooled sample to 200.0 ml with *water*. Further dilute a suitable volume of the solution with the solvent mixture to obtain a solution containing 0.0125 per cent w/v of pralidoxime chloride.

Reference solution (a). A 0.125 per cent w/v solution of *pralidoxime chloride IPRS* in *water*. Use sonication to dissolve, if necessary. *(NOTE – Pralidoxime chloride IPRS contains pralidoxime anti-isomer as a minor component)*

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

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

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm) (such as Zorbax 300 SB-C18),
- mobile phase: a mixture of 83 volumes of a buffer solution prepared by dissolving 1.87 g of *sodium octanesulphonate monohydrate* and 330 mg of *tetraethylammonium chloride* in 1000 ml of *water*, adjusted to pH 4.3 with *0.01 M hydrochloric acid* and 17 volumes of *acetonitrile*,
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 10 µl.

Name	Relative retention time	Correction factor
Pyridine-2-aldoxime	0.7	---
Pralidoxime anti-isomer[1]	0.9	---
Pralidoxime	1.0	---

[1](*Z*)-2-[(Hydroxyimino)methyl]-1-methylpyridin-1-ium chloride.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to pralidoxime anti-isomer and pralidoxime is not less than 2.0 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 pralidoxime chloride peak in the chromatogram obtained with reference solution (c).

Inject reference solution (c) and the test solution. In the chromatogram obtained with test solution, the area of any peak corresponding to pyridine-2-aldoxime is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent), the area of any peak corresponding to pralidoxime anti-isomer is not more than 20 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 30 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 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 (c) (0.05 per cent).

Uniformity of dosage units (2.5.4). Complies with the test stated under Uniformity of dosage units.

Loss on drying (2.4.19). Not more than 2.0 per cent, determined on 1.0 g by drying in an oven at 105° for 3 hours.

Bacterial endotoxins (2.2.3). Not more than 0.10 Endotoxin Unit per mg of pralidoxime chloride.

Sterility (2.2.11). Complies with the test for sterility.

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

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to pralidoxime anti-isomer and pralidoxime is not less than 2.0, 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 for pralidoxime chloride peak.

Inject reference solution (b) and the test solution.

Calculate the content of $C_7H_9ClN_2O$.

Storage. Store at a temperature not exceeding 30°.

Pregabalin Capsules. Page 3792

Related substances. After impurity table, para 2, line 3
Change **from**: not less than 13.
to: not less than 10.

Prochlorperazine Maleate. Page 3807

Change **to**: **Prochlorperazine Maleate**

$C_{20}H_{24}ClN_3S,2C_4H_4O_4$ Mol. Wt. 606.1

Prochlorperazine Maleate is 2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine maleate (1:2).

Prochlorperazine Maleate contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{20}H_{24}ClN_3S,2C_4H_4O_4$, calculated on the dried basis.

Category. Antipsychotic; antiemetic.

Description. A white or pale yellow, crystalline powder.

NOTE- Throughout the following procedures, protect the solutions from light, and conduct the procedures without delay.

Identification

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

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 40 volumes of *acetonitrile* and 60 volumes of *water*.

Test solution. Dissolve 64 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.016 per cent w/v solution of *prochlorperazine maleate IPRS* in the solvent mixture.

Reference solution (b). A 0.016 per cent w/v solution of *prochlorperazine related compound A IPRS* in the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 25.0 ml with the solvent mixture.

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

Reference solution (e). Dilute 1.0 ml of reference solution (c) to 20.0 ml with 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 XBridge C18),
- column temperature: 50º±5º,
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *sodium acetate trihydrate* in 1000 ml of *water*, add 2.0 ml of *triethylamine* and 6.0 ml of *glacial acetic acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
20	65	35
25	65	35
55	35	65
65	35	65

Name	Relative retention time	Correction factor*
Maleic acid	0.07	---
Prochlorperazine sulphoxide[1]	0.20	2.63
Perazine[2]	0.66	---
Prochlorperazine 4-chloro isomer (Prochlorperazine related compound A)[3]	0.97	1.64

Prochlorperazine	1.00	---
4-Chlorophenothiazine[4]	2.01	0.53
2-Chlorophenothiazine[5]	2.08	0.48
Specified unknown 1	2.64	---
Specified unknown 2	2.79	---
Specified unknown 3	2.88	---

*Correction factor is based on the response of prochlorperazine (free base),
[1]2-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine sulphoxide,
[2]10-[3-(4-Methylpiperazin-1-yl) propyl]-10*H*-phenothiazine,
[3]4-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine,
[4] 4-Chloro-10*H*-phenothiazine,
[5]2-Chloro-10*H*-phenothiazine.

Inject reference solution (c), (d) and (e). The test is not valid unless the resolution between the peaks due to prochlorperazine related compound A and prochlorperazine not less than 2.0 in the chromatogram obtained with reference solution (d), the relative standard deviation for replicate injections is not more than 5 per cent in the chromatogram obtained with reference solution (c) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (e).

Inject reference solution (c) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to prochlorperazine sulphoxide, perazine and prochlorperazine related compound A, each of, is not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.15 per cent), the area of any peak corresponding to 4-chlorophenothiazine and 2-chlorophenothiazine, each of, is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent), the area of any specified unknown 1 impurity and specified unknown 2 impurity, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.50 per cent), the area of any specified unknown 3 impurity, is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.20 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 (c) (0.10 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 (c) (1.5 per cent). Ignore any peak due to maleic acid and with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

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 in an oven at 60° for 2 hours.

Assay. Determine by liquid chromatography (2.4.14).

Buffer solution. Dissolve 4.33 g of *octanesulphonic acid sodium salt* in 500 ml of *water*, add 4.0 ml of *glacial acetic acid* and dilute to 1000 ml with *water*.

Test solution. Dissolve 20 mg of the substance under examination in the mobile phase with the aid of ultrasound and dilute to 100.0 ml with the mobile phase.

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

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Inertsil ODS-3),
- mobile phase: a mixture of 40 volumes of *acetonitrile*, 45 volumes of the buffer solution and 15 volumes of *methanol*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 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 of replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{24}ClN_3S,2C_4H_4O_4$.

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

Prochlorperazine Tablets. Page 3808

Change **to**: **Prochlorperazine Tablets**

Prochlorperazine Maleate Tablets

Prochlorperazine Tablets contain prochlorperazine maleate equivalent to not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of prochlorperazine, $C_{20}H_{24}ClN_3S$.

Usual strengths. 5 mg; 25 mg.

NOTE- Throughout the following procedures, protect the solutions from light, and conduct the procedures without delay.

Identification

A. To a quantity of the powdered tablets containing 40 mg of Prochlorperazine Maleate, add 10 ml of *water* and 2 ml of *1 M sodium hydroxide*, shake and extract with 15 ml of *ether*. Wash the ether layer with 5 ml of *water*, filter the ether layer through *anhydrous sodium sulphate*, evaporate to dryness and dissolve the residue in 0.4 ml of *chloroform*. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *prochlorperazine maleate IPRS*, treated in the same manner or with the reference spectrum of prochlorperazine.

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

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium: 500 ml of *0.1M hydrochloric acid*,
Speed and time. 75 rpm for 60 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtrate, dilute suitably, if necessary, with the medium, at the maximum at about 254 nm (2.4.7). Calculate the content of prochlorperazine, $C_{20}H_{24}ClN_3S$ in the medium from the absorbance obtained from a solution of known concentration of *prochlorperazine maleate IPRS* in the dissolution medium.

Q. Not less than 75 per cent of the stated amount of $C_{20}H_{24}ClN_3S$.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 40 volumes of *acetonitrile* and 60 volumes of *water*.

Test solution. Transfer 20 intact tablets to a suitable volumetric flask, add solvent mixture (80 per cent of the final volume) and disperse with the aid of ultrasound with occasional swirling for 10 minutes and dilute to volume with the solvent mixture to obtain a solution containing 0.04 per cent w/v of prochlorperazine. Centrifuge a portion the solution and use the supernatant liquid.

Reference solution (a). A 0.016 per cent w/v solution of *prochlorperazine maleate IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 25.0 ml with the solvent mixture.

Reference solution (c). A 0.016 per cent w/v solution of *prochlorperazine related compound A IPRS* in the solvent mixture.

Reference solution (d). Dilute 1.0 ml, each of, reference solution (a) and reference solution (c) to 100.0 ml with 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 XBridge C18),
- column temperature: 50º±5º,
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *sodium acetate trihydrate* in 1000 ml of *water*, add 2.0 ml of *triethylamine* and 6.0 ml of *glacial acetic acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
20	65	35
25	65	35
55	35	65
65	35	65

Name	Relative retention time	Correction factor
Maleic acid	0.07	---
Prochlorperazinesulphoxide[1]	0.20	2.63
Perazine[2*]	0.66	---
Prochlorperazine related compound A[3*]	0.97	---
Prochlorperazine	1.00	---
4- Chlorophenothiazine[4*]	2.01	---
2- Chlorophenothiazine[5*]	2.08	---
Specified unknown 1[*]	2.64	---
Specified unknown 2[*]	2.79	---
Specified unknown 3[*]	2.88	---

*Process impurity included for identification purpose only, it not to be calculated and included in total degradation products.
[1]2-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine sulphoxide,
[2]10-[3-(4-Methylpiperazin-1-yl) propyl]-10*H*-phenothiazine,
[3]4-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine dihydrochloride,
[4]4-Chloro-10*H*-phenothiazine,
[5]2-Chloro-10*H*-phenothiazine.

Inject reference solution (b) and (d). The test is not valid unless the resolution between the peak prochlorperazine related compound A and prochlorperazine is not less than 2.0 in the chromatogram obtained with reference solution (d) and the relative standard deviation of 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 prochlorperazine sulphoxide is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 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) (0.5 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) (2.0 per cent). Ignore any peak due to maleic acid and with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Uniformity of dosage units (2.5.4). Complies with the tests stated under Uniformity of dosage units (2.5.4).

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

Buffer solution. Dissolve 4.33 g of *octanesulphonic acid sodium salt* in 500 ml of *water*, add 4.0 ml of *glacial acetic acid* and dilute to 1000 ml with *water*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of powder containing 12 mg of prochlorperazine in the mobile phase, with the aid of ultrasound for 5 minutes and shake by mechanical means for 30 minutes, dilute to 100.0 ml with the mobile phase and filter.

Reference solution. A solution of *prochlorperazine maleate IPRS* containing 0.012 per cent w/v of prochlorperazine in the mobile phase.

Chromatographic system
- a stainless steel column 30 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (10 µm) (such as MicroBondapak C18),
- mobile phase: a mixture of 45 volumes of the buffer solution, 40 volumes of *acetonitrile* and 15 volumes of *methanol,*
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 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 of replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{24}ClN_3S$ in the tablets.

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

Labelling. The label states the strength in terms of the equivalent amount of prochlorperazine.

Ramipril Capsules. Page 3918

Related substances. Chromatographic system
Insert before mobile phase
- column temperature: 60°,

Ramipril Tablets. Page 3919

Related substances. Chromatographic system
Insert before mobile phase
- column temperature: 60°,

Rosuvastatin Calcium. Page 3998

Related substances. Impurity table, line 3
Change **from**: Rosuvastatin diastereomers[2]
to: Rosuvastatin related compound B (rosuvastatin diastereomers)[2]

Rosuvastatin Tablets. Page 4000

Related substances. *Reference solution (c),* line 1
Change **from**: 0.0001 per cent
to: 0.1 per cent

Sertraline Tablets. Page 4050

Related substances. *Test solution*, line 1 and 2
Change **from**: Disperse a quantity of whole tablets containing 500 mg of Sertraline Hydrochloride
to: Disperse a quantity of whole tablets containing 500 mg of Sertraline

Reference solution (a)
Change **from**: A 0.0005 per cent w/v solution of *sertraline hydrochloride IPRS* in the solvent mixture.
to: A solution of *sertraline hydrochloride IPRS* equivalent to 0.0005 per cent w/v of *sertraline* in the solvent mixture.

Reference solution (c), line 2
Change **from**: *sertraline hydrochloride impurity IPRS* in solvent mixture.
to: *sertraline hydrochloride impurity standard IPRS* (containing sertraline impurity C) in solvent mixture.

After gradient programme, line 1 and 2
Change **from**: Inject reference solution (c). For peak identification of sertraline hydrochloride impurity.
to: Inject reference solution (c) to identify the peak due to sertraline impurity C.

Last para, line 2 to 7
Change **from**: the sum of areas of any peaks corresponding to sertraline impurity C (1*RS*, 4*RS*)-4-(4-chlorophenyl)_*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine) and sertraline impurity D (1*RS*, 4*RS*)-4-(3-chlorophenyl)_*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine)
to: the areas of any peak corresponding to sertraline impurity C (1*RS*, 4*RS*)-4-(4-chlorophenyl)_*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine)

Assay. *Test solution*, line 2 to 3
Change **from**: 0.2 g of Sertraline Hydrochloride
to: 0.2 g of Sertraline

Sodium Valproate Oral Solution. Page 4111

Related substances. Change **to**:
Related substances. Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.005 per cent w/v of *octanoic acid* in *dichloromethane*.

Test solution. Shake a quantity of the oral solution containing 0.5 g of Sodium Valproate with 80 ml of *water*, acidify with 1 ml of *2 M sulphuric acid*. Mix the solution and add 10.0 ml of the internal standard solution and extract with three quantities, each of, 20 ml of *dichloromethane* and combine the organic layers. Dry the combined organic layer by shaking with *anhydrous sodium sulphate*, filter. Reduce the volume of the filtrate at a temperature not exceeding 30° and dilute to 10.0 ml with *dichloromethane*.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the internal standard solution. Dilute 1.0 ml of the solution to 10.0 ml with the internal standard solution.

Reference solution (b). A 5 per cent w/v solution of *valproic acid for system suitability IPRS* in *dichloromethane*.

Chromatographic system
– a fused silica column 30 m × 0.53 mm, packed with macrogol 20000 2-nitroterephthalate (film thickness 0.5 µm) (such as DB-FFAP),
– temperature:

column	time (min.)	temperature (°)
	0-5	80
	5-15	80-150
	15-28.3	150-190
	28.3-30	190
	30-35	190-250
	35-45	250

– inlet port at 220° and detector at 220°,
– flame ionisation detector,
– split ratio: 1:10,
– flow rate: 8 ml per minutes, using helium as carrier gas,
– injection volume: 1µl.

Name	Relative retention time
Valproic acid impurity K[1]	0.97

Valproic acid (retention time: about 15 minutes)	1.0
Octanoic acid	1.12

[1](2*RS*)-2-ethyl-2-methylpentanoic acid.

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

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the ratio of the area of the peak due to valproic acid impurity K to the area of the peak due to the internal standard is not more than twice the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.2 per cent), the ratio of the area of any other secondary peak to the area of the peak due to the internal standard is not more than the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.1 per cent) and the ratio of the sum of the areas of all the secondary peaks to the area of the peak due to the internal standard is not more than 4 times the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.4 per cent). Ignore any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not more than 0.5 times the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard peak in the chromatogram obtained with reference solution (a) (0.05 per cent) and any peak eluting after 30 minutes.

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

NOTE – Use freshly prepared solutions.

Test solution. Transfer a weighed quantity of the oral solution containing 0.16 g of Sodium Valproate to a 50-ml volumetric flask, add 1 ml of 10 per cent v/v solution of *orthophosphoric acid* and dilute to volume with the mobile phase.

Reference solution (a). Dissolve 0.16 g of *sodium valproate IPRS* in 15 ml of the mobile phase, add 1 ml of a 10 per cent v/v solution of *orthophosphoric acid*, mix and dilute to 50.0 ml with the mobile phase.

Reference solution (b). A 0.002 per cent w/v solution of *propyl 4-hydroxybenzoate* in reference solution (a).

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (10 µm) (such as Spherisorb ODS 1),
- mobile phase: a mixture of 35 volumes of *0.05 M potassium dihydrogen orthophosphate* and 65 volumes of *methanol*, adjusted to pH 5.0 with 10 per cent v/v solution of *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to propyl 4-hydroxy benzoate and valproic acid is not less than 2.0

Inject reference solution (a) and the test solution.

Determine weight per ml (2.4.29) of the oral solution and calculate the content of $C_8H_{15}NaO_2$ in the oral solution.

Sodium Valproate Gastro-resistant Tablets. Page 4113

Related substances. Change **to**:
Related substances. Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.005 per cent w/v solution of *octanoic acid* in *dichloromethane*.

Test solution. Disperse a quantity of the powdered tablets containing 1 g of Sodium Valproate with 20 ml of *0.1 M sodium hydroxide* with the aid of ultrasound for 30 minutes and centrifuge. Transfer 10.0 ml of supernatant into

a separating funnel, add 1 ml of *2 M sulphuric acid* and 10.0 ml of the internal standard solution. Extract the mixture with three quantities, each of, 20 ml of *dichloromethane*. Dry the extracts over *anhydrous sodium sulphate*, filter and evaporate the filtrate to dryness at a temperature not exceeding 30° and dilute to 10.0 ml with *dichloromethane*.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the internal standard solution. Dilute 1.0 ml of the solution to 10.0 ml with the internal standard solution.

Reference solution (b). A 5 per cent w/v solution of *valproic acid for system suitability IPRS* in *dichloromethane*.

Chromatographic system
– a fused silica column 30 m × 0.53 mm, packed with macrogol 20000 2-nitroterephthalate (film thickness 0.5 µm) (such as DB-FFAP),
– temperature:

column	time (min.)	temperature (°)
	0-5	80
	5-15	80-150
	15-28.3	150-190
	28.3-30	190
	30-35	190-250
	35-45	250

– inlet port at 220° and detector at 220°,
– flame ionisation detector,
– split ratio: 1:10,
– flow rate: 8 ml per minutes, using helium as carrier gas,
– injection volume: 1µl.

Name	Relative retention time
Valproic acid impurity K[1]	0.97
Valproic acid (retention time: about 15 minutes)	1.0
Octanoic acid	1.12

[1](2*RS*)-2-ethyl-2-methylpentanoic acid.

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

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the ratio of the area of the peak due to valproic acid impurity K to the area of the peak due to the internal standard is not more than twice the ratio of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.2 per cent), the ratio of the area of any other secondary peak to the area of the peak due to the internal standard is not more than the ratio of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.1 per cent) and the ratio of the sum of the areas of all the secondary peaks to the area of the peak due to the internal standard is not more than 4 times the ratio of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.4 per cent). Ignore any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not more than 0.5 times the ratio of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.05 per cent) and any peak eluting after 30 minutes.

Sodium Valproate Tablets. Page 4112

Dissolution. Change **to**:
Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 900 ml of *phosphate buffer* pH 6.8,
Speed and time. 50 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Use the filtrate, dilute if necessary, with the dissolution medium.

Reference solution. Dissolve a quantity of *sodium valproate IPRS* in the dissolution medium to obtain a solution having a known concentration similar to the expected concentration of the test solution.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with base-deactivated end-capped octadecylsilane bonded to porous silica (5 µm) (such as Hypersil BDS C18),
- column temperature: 25°,
- mobile phase: a mixture of 50 volumes of a buffer solution prepared by dissolving 1.56 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 2.3 with *orthophosphoric acid* and 50 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_8H_{15}NaO_2$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_8H_{15}NaO_2$.

Related substances. Change **to**:
Related substances. Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.005 per cent w/v of *octanoic acid* in *dichloromethane*.

Test solution. Disperse a quantity of the powdered tablets containing 1 g of Sodium Valproate with 20 ml of *0.1 M sodium hydroxide* with the aid of ultrasound for 30 minutes and centrifuge. Transfer 10.0 ml of supernatant into a separating funnel, add 1 ml of *2 M sulphuric acid* and 10.0 ml of the internal standard solution. Extract the mixture with three quantities, each of, 20 ml of *dichloromethane*. Dry the extracts over *anhydrous sodium sulphate*, filter and evaporate the filtrate to dryness at a temperature not exceeding 30° and dilute to 10.0 ml with *dichloromethane*.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the internal standard solution. Dilute 1.0 ml of the solution to 10.0 ml with the internal standard solution.

Reference solution (b). A 5 per cent w/v solution of *valproic acid for system suitability IPRS* in *dichloromethane*.

Chromatographic system
- a fused silica column 30 m × 0.53 mm, packed with macrogol 20000 2-nitroterephthalate (film thickness 0.5 µm) (such as DB-FFAP),
- temperature:

column	time (min.)	temperature (°)
	0-5	80
	5-15	80-150
	15-28.3	150-190
	28.3-30	190
	30-35	190-250
	35-45	250

- inlet port at 220° and detector at 220°,
- flame ionisation detector,
- split ratio: 1:10,

– flow rate: 8 ml per minutes, using helium as carrier gas,
– injection volume: 1µl.

Name	Relative retention time
Valproic acid impurity K[1]	0.97
Valproic acid (retention time: about 15 minutes)	1.0
Octanoic acid	1.12

[1](2*RS*)-2-ethyl-2-methylpentanoic acid.

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

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the ratio of the area of the peak due to valproic acid impurity K to the area of the peak due to the internal standard is not more than twice the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.2 per cent), the ratio of the area of any other secondary peak to the area of the peak due to the internal standard is not more than the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.1 per cent) and the ratio of the sum of the areas of all the secondary peaks to the area of the peak due to the internal standard is not more than 4 times the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.4 per cent). Ignore any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not more than 0.5 times the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard in the chromatogram obtained with reference solution (a) (0.05 per cent) and any peak eluting after 30 minutes.

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

Solution A. Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 6.8 with *0.2 M sodium hydroxide*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 0.5 g of Sodium Valproate in 50 ml *acetonitrile*, add 100 ml of solution A with the aid of ultrasound and dilute to 200.0 ml with solution A and filter. Dilute 2.0 volume of the solution to 10.0 volumes with solution A.

Reference solution. Dissolve 50 mg of *sodium valproate IPRS* in 5 ml of *acetonitrile*, add 10 ml of solution A with the aid of ultrasound and dilute to 100.0 ml with solution A.

Use chromatographic system as described under Dissolution.

Inject the reference solution and the test solution.

Calculate the content of $C_8H_{15}NaO_2$ in the tablets.

Sorbitol. Page 4130

Nickel
Change **to: Nickel.** Note more than 1 µg per g.
Determine by Inductively Coupled Plasma Spectrometry (2.4.42).

NOTE- When water is specified as the diluent, use deionized ultra-filtered water. Avoid use of glass volumetric flasks.

Digest solution. Mix 360 ml of *hydrochloric acid, ultratrace* and 240 ml of *nitric acid, ultratrace* with 1200 ml of *water*.

Blank solution. Add 40 ml of *nitric acid, ultratrace* to a 2000-ml volumetric flask, and dilute to volume with *water*, and mix well.

Internal standard solution. Transfer 2.0 ml of a solution containing 1000 mg per litter of *yttrium* ICP standard solution to a 1000-ml volumetric flask, dilute to volume with the blank solution, and mix well. The internal standard solution contains 2 µg per ml of *yttrium*. *[NOTE—The concentration of the internal standard solution can be adjusted if a high number of signal counts from the internal standard solution causes an artifact.]*

Test solution. Transfer 10.0 g of substances under examination into a 125-ml conical flask. Add 40 ml of the digest solution, and place on a hot plate. Heat the solution for about 20 minutes, being careful to prevent the solution from boiling over. Pull the solution off of the hot plate just before it turns a dark caramel colour. *(Note—Do not overburn the solution.)* Transfer the flask's contents into a clean, dry, 50-ml volumetric flask with washings of the blank solution, dilute to volume with the blank solution. Filter this solution into a 15-ml centrifuge tube, with a syringe filter through a 0.45 µm filter.

Reference solution (a). Quantitatively dilute an accurately measured volume of a solution containing 1000 mg per litter of *nickel* with the blank solution to obtain a solution containing 10 µg per ml of *nickel*. *[NOTE—Prepare this solution fresh every 2 months.]*

Reference solution (b). Pipet 1.0 ml of reference solution (a) into a 200-ml volumetric flask, dilute to volume with the blank solution, and mix well. This solution contains 50 ng per ml of *nickel*. *[NOTE—Prepare this solution fresh weekly.]*

Reference solution (c). Pipet 2.0 ml of the reference solution (a) into a 200-ml volumetric flask, dilute to volume with the blank solution, and mix well. This solution contains 100 ng per ml of *nickel*. *[NOTE—Prepare this solution fresh weekly.]*

Reference solution (d). Pipet 4.0 ml of the reference solution (a) into a 200-ml volumetric flask, dilute to volume with the blank solution, and mix well. This solution contains 200 ng per ml of *nickel. [NOTE—Prepare this solution fresh weekly.]*

NOTE- Yttrium ICP standard solutions and Nickel ICP standard solutions are commercially available.

*Emission wavelengths.*232.005 nm for nickel and 371.029 nm for yttrium. Set the sample read time and other instrument parameters as appropriate or as recommended by the instrument manufacturer.

Inject the blank solution, reference solution (b), (c) and (d).

The test is not valid unless the correlation coefficient is not less than 0.999, determined from the calibration curve constructed in the analysis

NOTE—Instrument performance must be verified to conform to the manufacturer's specifications for resolution and sensitivity. Before analysing samples, the instrument must pass a suitable performance check.

Analysis. Inject the blank solution, reference solution (b), (c), (d) and test solution.

NOTE—The following analysis is described for one type of ICP–OES instruments. If a different ICP–OES instrument is used, follow the instrument manufacturer's recommendations for operation.

Take three replicate scans with the integration set as recommended by the instrument manufacturer. Follow the instrument manufacturer's recommendations for delivering the test solution. Add the internal standard solution in-line via a mixing block between the sample probe and the spray chamber. Flush the samples through the system before analysis. Program a read delay into the sampling routine to allow for fluid flow equilibration after the high-speed flush, before the first analytical read of the test solution. Between solutions, wash the pumping system by flushing the blank solution.

Calibration curve. Generate the calibration curve using the blank solution, reference solution (b), reference solution (c) and reference solution (d) as follows. Scan the internal standard solution while running the blank solution to measure the intensity of the yttrium emission. Hold this value constant throughout the remainder of

the test. Separately scan the blank solution, reference solution (b), reference solution (c) and reference solution (d) for nickel and yttrium. *(Note—Add the internal standard solution via an in-line mixing chamber.)* Normalize the yttrium intensity to the value of the internal standard solution. Apply this normalization factor to the nickel intensity, which is then referred to as the corrected nickel intensity. Construct a calibration curve by plotting the corrected nickel intensity versus the known concentrations, in ng per ml, of the nickel.

Similarly, analyse the test solution. Plot the intensity of the emission of the test solution on the calibration curve. Determine the concentration of nickel (*C*), in ng per ml, in the test solution through the calibration curve.

Calculate the content, in µg per g, of nickel in the portion of substances taken:

$$\text{Result} = (F \times V \times C)/W$$

F = conversion factor, 10^{-3} µg per ng (ng to µg)

V = volume of the test solution, 50 ml

C = concentration of nickel in the test solution (ng per ml)

W = weight of substances under examination (g).

Tenofovir Disoproxil Fumarate Tablets. Page 4233

Related substances. *Reference solution (a)*, line 3
Change **from**: the solvent mixture.
to: mobile phase A.

Triprolidine Hydrochloride. Page 4379

Change **to**: **Triprolidine Hydrochloride**

$C_{19}H_{22}N_2,HCl,H_2O$ Mol. Wt. 332.9
$C_{19}H_{22}N_2,HCl$ Mol. Wt. 314.9

Triprolidine Hydrochloride is (*E*)-2-[3-(1-Pyrrolidinyl)-1-*p*-tolylpropenyl]pyridine monohydrochloride; (*E*)-2-[3-(1-Pyrrolidinyl)-1-*p*-tolylpropenyl]pyridine monohydrochloride monohydrate.

Triprolidine Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{19}H_{22}N_2,HCl$, calculated on the anhydrous basis.

Category. Histamine H_1-receptor antagonist.

Description. A white, crystalline powder.

Identification

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

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

C. A 5 per cent w/v solution gives the reaction (A) of chlorides (2.3.1).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 20 volumes of *acetonitrile* and 80 volumes of *water.*

Test solution (a). Dissolve 25 mg of the substance under examination in the solvent mixture, with the aid of ultrasound and dilute to 25.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 10.0 ml with the solvent mixture.

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

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

Reference solution (b). A solution containing 0.001 per cent w/v solution, each of, *triprolidine hydrochloride IPRS* and *triprolidine hydrochloride Z-isomer IPRS* 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),
- column temperature: 45º,
- mobile phase: a mixture of 20 volumes of *acetonitrile* with 80 volumes of *water* and 0.1 volumes of *formic acid,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Name	Relative retention time
Triprolidine	1.0
Triprolidine hydrochloride *Z*-isomer[1]	1.5

[1](*Z*)-2-[3-(1-Pyrrolidinyl)-1-*p*-tolylpropenyl]pyridine monohydrochloride.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to triprolidine hydrochloride and triprolidine hydrochloride *Z*-isomer is not less than 5.0 and the relative standard deviation for replicate injections is not more than 1.8 per cent, for each peak.

Inject reference solution (b) and test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to triprolidine hydrochloride *Z*-isomer is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (2.0 per cent), the area of any other secondary peak is not more than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 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 (b) (3.0 per cent).

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

Water (2.3.43). Not more than 0.5 per cent (for anhydrous form) and 4.0 to 6.0 per cent (for monohydrate form), determined on 0.4 g.

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

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to triprolidine hydrochloride and triprolidine hydrochloride *Z*-isomer is not less than 5.0 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 reference solution (a) and test solution (b).

Calculate the content of $C_{19}H_{22}N_2$,HCl.

Storage. Store protected from light and moisture.

Triprolidine Tablets. Page 4380

Change **to**: **Triprolidine Tablets**

Triprolidine Hydrochloride Tablets

Triprolidine Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of triprolidine hydrochloride, $C_{19}H_{22}N_2$,HCl,H_2O.

Usual strength. 10 mg.

Identification

A. Extract a quantity of the powdered tablets containing 10 mg of Triprolidine Hydrochloride with *ether*, filter, discard the ether extract and dry the residue. Extract the residue with *chloroform*, filter and evaporate the filtrate to dryness. Add 0.1 ml of *ether*, stir and allow to evaporate. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *triprolidine hydrochloride IPRS* or with the reference spectrum of triprolidine 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

Dissolution (2.5.2).
Apparatus No .1 (Basket),
Medium. 500 ml of acetate buffer pH 4.0 prepared by dissolving 2.45 g of *sodium acetate trihydrate* and 4.9 g of *glacial acetic acid* in 1000 ml of *water*, adjusted to pH 4.0,
Speed and time. 50 rpm, 30 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtrate, dilute suitably if necessary with the medium, at the maximum at about 277 nm (2.4.7). Calculate the content of $C_{19}H_{22}N_2$,HCl,H_2O in the medium from the absorbance obtained from a solution of known concentration of *triprolidine hydrochloride IPRS* in the dissolution medium.

Q. Not less than 80 per cent of the stated amount of $C_{19}H_{22}N_2$,HCl,H_2O.

Uniformity of dosage units (2.5.4). Complies with the tests stated under Uniformity of dosage units.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 5 mg of Triprolidine Hydrochloride in *0.01 M hydrochloric acid* with the aid of ultrasound for 10 minutes, cool and dilute to 100.0 ml with *0.01 M hydrochloric acid*, filter.

Reference solution. A 0.005 per cent w/v solution of *triprolidine hydrochloride IPRS* in *0.01 M hydrochloric acid*.

Chromatographic system
- a stainless steel column 25 cm x 4.2 mm, packed with porous silica particles (10 µm) (such as Partisil 10 Silica),
- mobile phase: a mixture of 85 volumes of *ethanol (95 per cent)* and 15 volumes of 0.4 per cent w/v solution of *ammonium acetate*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

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 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{19}H_{22}N_2$,HCl,H_2O in the tablets.

1 mg of triprolidine hydrochloride, $C_{19}H_{22}N$,HCl is equivalent to 1.057 mg of triprolidine hydrochloride monohydrate, $C_{19}H_{22}N$,HCl,H_2O.

Storage. Store protected from light and moisture.

Ursodeoxycholic Acid. Page 4400
Identification. B, line 1 and 3
Change **from**: spot
to: peak

Vildagliptin and Metformin Prolonged-release Tablets. Page 4451
Related substances
For Metformin Hydrochloride -
Reference solution (b), line 2
Insert at the end
Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Xanthan Gum. Page 4487
Viscosity. Line 12
Change **from**: diameter and .6 mm high
to: diameter and 1.6 mm high

VETERINARY PRODUCTS

Ampicillin Injection. Page 5355
Title Change **to**:
Ampicillin for Injection

Moxidectin. Page 5427
Related substances. A
After Impurity Table**,** IUPAC names
Change **to**:
[1](6*R*,23*E*,25*S*)-25-[(2*E*)-but-2-en-2-yl]-5-O-demethyl-28-deoxy-6,28-epoxy-23-(methoxyimino)milbemycin B,
[2](6*R*,23*E*,25*S*)-5-*O*,24-didemethyl-28-deoxy-6,28-epoxy-23-(methoxyimino)-25-[(2*E*)-4-methylpent-2-en-1-yl]milbemycin B,
[3](6*R*,23*E*,25*S*)-5-*O*-demethyl-28-deoxy-6,28-epoxy-23-(methoxyimino)-25-[(2*E*)-pent-2-en-1-yl]milbemycin B,
[4](6*R*,23*E*,25*S*)-5-*O*-demethyl-28-deoxy-6,28-epoxy-23-(methoxyimino)-25-[(2*E*)-4-methylpent-2-en-1-yl]-2-*epi*-milbemycin B,
[5](1[6]*S*,6*R*,23*E*,25*S*)-5-*O*-demethyl-28-deoxy-6,28-epoxy-23-(methoxyimino)-25-[(2*E*)-4-methylpent-2-en-1-yl]-1[4]-dehydro-1[6]-hydromilbemycin B,
[6]one of groups R1 to R6 is C_2H_5, the others are CH_3: x-demethyl-x-ethylmoxidectin,
[7](23*E*,25*S*)-5-*O*-demethyl-28-deoxy-23-(methoxyimino)-25-[(2*E*)-4-methylpent-2-en-1-yl]milbemycin B.

B.
After Impurity Table**,** IUPAC names
Change **to**:
[8](6*R*,23*E*,25*S*)-5-demethoxy-28-deoxy-6,28-epoxy-23-(methoxyimino)-25-[(2*E*)-4-methylpent-2-en-1-yl]-2,5-didehydromilbemycin B,
[9](6*R*,23*E*,25*S*)-5-*O*-demethyl-28-deoxy-6,28-epoxy-25-[(2*E*)-4-methylpent-2-en-1-yl]-23-[(methylsulfanyl)methoxy]milbemycin B,
[10](6*R*,23*E*,25*S*)-5-*O*-demethyl-28-deoxy-6,28-epoxy-23-(methoxyimino)-25-[(2*E*)-4-methylpent-2-en-1-yl]-7-*O*-[(methylsulfanyl)methyl]milbemycin B,
[11](6*R*,23*E*,25*S*)-5-*O*-demethyl-28-deoxy-6,28-epoxy-23-(methoxyimino)-25-[(2*E*)-4-methylpent-2-en-1-yl]-5-*O*-(4-nitrobenzoyl)milbemycin B,

Moxidectin Injection. Page 5429
Insert before **Other tests**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of the injection, if necessary, with *water* to produce a solution containing 0.1 per cent w/v of moxidectin. To 2 ml of the solution, add 20 ml of 0.5 per cent w/v solution of *sodium chloride* and 15 ml of *dichloromethane*, mix. Centrifuge the mixture and separate the two layers. Repeat the extraction of the upper aqueous layer plus any suspended solids with a further 5 ml of *dichloromethane*. To the combined dichloromethane layers, add 1 g of *sodium sulphate*, shake and filter. Dilute the filtrate to 25 ml with *dichloromethane*.

Prepare a solid phase extraction cartridge containing a silica sorbent (such as: Varian Mega Bond Elut cartridges) by passing 50 ml of *acetonitrile* (followed by 20 ml of *dichloromethane*) through the cartridge under gravity. Pass

2 ml of the diluted filtrate through the cartridge under vacuum (followed by 20 ml of dichloromethane) discarding the eluent. Pass 6 ml of *acetonitrile* through the cartridge under gravity and collect the eluent. Force through any residual *acetonitrile* under vacuum. Dilute the eluent to 5.0 ml with *acetonitrile*.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with *acetonitrile*.

Reference solution (b). A 0.25 per cent w/v solution of *moxidectin for system suitability IPRS* in *acetonitrile*.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 10.0 ml with *acetonitrile*.

Chromatographic system

- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (4 µm) (such as Novapak C18),
- column temperature: 50°,
- mobile phase: A. a 0.7 per cent w/v solution of *ammonium acetate*, adjusted to pH 6.0 with *glacial acetic acid* or *ammonium hydroxide*,
  B. *acetonitrile*,
- flow rate: 2.5 ml per minute,
- spectrophotometer set at 242 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase (per cent v/v)	Mobile phase (per cent v/v)
0	60	40
50	20	80
55	20	80
56	60	40
65	60	40

Name	Relative retention time
Moxidectin impurity D[1]	0.98
Moxidectin	1.0

[1](6*R*,23*E*,25*S*)-5-*O*-demethyl-28-deoxy-6,28-epoxy-23-(methoxyimino)-25-[(2*E*)-4-methylpent-2-en-1-yl]-2-*epi*-milbemycin B.

Inject reference solution (b). The test is not valid unless the peak to valley ratio (Hp/Hv) is not less than 2.0, where Hp is the height above the baseline of the peak due to moxidectin impurity D and Hv is the height above the baseline of the lowest point of the curve separating this peak due to moxidectin.

Inject reference solution (a), (c) and the test solution. In the chromatogram obtained with the test solution, 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) (1.0 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 (a) (7.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Insert at the end
Storage. Store protected from Light.