Micafungin for Injection

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. 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 lab.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.	

Micafungin for Injection

Micafungin for Injection is a sterile lyophilized powder consisting of Micafungin Sodium with or without excipients. It is filled 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 or suitable solvent, immediately before use.

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

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

Micafungin for Injection contains micafungin sodium equivalent to not less than 95.0 per cent and not more than 115.0 per cent of the stated amount of micafungin, $C_{56}H_{71}N_9O_{23}S$.

Usual strengths. 50 mg per vial, 100 mg per vial.

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

Identification

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

Tests

pH (2.4.24). 5.0 to 7.0, determined in a 1.0 per cent w/v solution constituted as directed in the labelling.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Carry out the tests protected from direct sunlight and use light-resistant glasswares.

Solvent mixture. 66 volumes of a buffer solution prepared by dissolving 35.8 g of *disodium hydrogen orthophosphate, dodecahydrate* in 1000 ml *water* and 33 volumes of a buffer solution prepared by dissolving 13.6 g of *potassium dihydrogen orthophosphate* in 1000 ml water, adjusted to pH 7.0.

Test solution. Reconstitute 5 vials with the solvent mixture as directed in the labelling and pool the contents of 5 vials and prepare a composite sample. Dilute a suitable volume of the pooled sample with the solvent mixture to obtain a solution containing 0.4 per cent w/v of Micafungin.

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

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 3.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution 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 YMC-Pack ODS-AM)
- column temperature: 35°,
- mobile phase: a mixture of 45 volumes of *acetonitrile* and 70 volumes of a buffer solution prepared by dissolving 18.7 g of *sodium dihydrogen phosphate dihydrate* and 7.7 g of *sodium perchlorate* in 1000 ml of *water*, adjusted to pH 3.0 with 10 per cent v/v solution of *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 2 µl.

Name	Relative retention time
Micafungin open ring analog[1]	0.73

Desmethyl micafungin[2]	0.91
Micafungin serine analog[3]	0.91
Micafungin	1.00
Micafungin epimer[4]	1.09
Deoxy micafungin[5]	1.12

[1]Sodium5-[(1*S*,2*S*,3*S*)-4-({(2*S*,3*R*)-5-amino-1-[(2*S*,3*S*,4*S*)-2-carbamoyl-3-hydroxy-4-methylpyrrolidin-1-yl]-3-hydroxy-1,5-dioxopentan-2-yl}amino)-3-[(2*S*,4*R*)-1-{[(2*S*,4*R*)-4,5-dihydroxy-1-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzoyl)pyrrolidine-2-carbonyl]-l-threonyl}-4-hydroxypyrrolidine-2-carboxamido]-1,2-dihydroxy-4-oxobutyl]-2-hydroxyphenyl sulfate,
[2]Sodium5-[(1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,11*R*,12*R*,14a*S*,15*S*,20*S*,23*S*,25a*S*)-20-[(*R*)-3-amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(*R*)-1-hydroxyethyl]-5,8,14,19,22,25-hexaoxo-9-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzamido)tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl]-2-hydroxyphenyl sulphate,
[3]Sodium5-[(1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,11*R*,12*R*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(*R*)-3-amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-(hydroxymethyl)-16-methyl-5,8,14,19,22,25-hexaoxo-9-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzamido)tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate,
[4]Sodium5-[(1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,11*R*,12*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(*R*)-3-amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(*R*)-1-hydroxyethyl]-16-methyl-5,8,14,19,22,25-hexaoxo-9-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzamido)tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate,
[5]Sodium5-[(1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,12*R*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(*R*)-3-amino-1-hydroxy-3-oxopropyl]-2,12,15-trihydroxy-6-[(*R*)-1-hydroxyethyl]-16-methyl-5,8,14,19,22,25-hexaoxo-9-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzamido)tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to micafungin and micafungin epimer is not less than 1.2 in the chromatogram obtained with reference solution (a), the tailing factor is not more than 1.5, the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to micafungin open ring analog and micafungin epimer, each of, is not more than 3.66 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.1 per cent), the sum of area of the peak corresponding to desmethyl micafungin and micafungin serine analog is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.2 per cent), the area of any peak corresponding to deoxy micafungin is not more than 1.66 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 the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent) and the sum of the areas of all the secondary peaks is not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (4.5 per cent). Ignore any peak with an area less than 0.166 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Bacterial endotoxins (2.2.3). Not more than 2 Endotoxin unit per mg of micafungin.

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

Assay. Determine by liquid chromatography (2.4.14).

NOTE- Carry out the tests protected from direct sunlight and use light-resistant glasswares.

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

Test solution. Reconstitute 5 vials with the solvent mixture as directed in the labelling and pool the contents of 5 vials and prepare a composite sample. Dilute a suitable volume of the pooled sample with the solvent mixture to obtain a solution containing 0.05 per cent w/v of Micafungin.

Reference solution. A solution of *micafungin sodium IPRS* containing 0.05 per cent w/v of micafungin in the solvent mixture.

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

– injection volume: 5 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 $C_{56}H_{71}N_9O_{23}S$ in the injection.

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

Labelling. The label states the quantity of micafungin sodium contained in the sealed container in the terms of the equivalent amount of micafungin.