Miltefosine Capsules

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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.	

Miltefosine Capsules

Miltefosine Capsules contain not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of miltefosine, $C_{21}H_{46}NO_4P$.

Usual strengths. 50 mg.

Identification

A. Shake a quantity of the mixed contents of the capsules containing 0.25 g of Miltefosine with 25 ml of *chloroform* for 15 minutes. Pass the *chloroform* layer through *sodium sulphate anhydrous* and evaporate to dryness. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *miltefosine IPRS* or with the reference spectrum of miltefosine.

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. 750 ml of *0.01 M hydrochloric acid,*
Speed and time. 50 rpm and 15 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of dissolution medium and *water*.

Test solution. Use the filtrate, dilute 5.0 ml of the filtrate to 10.0 ml with *acetonitrile*.

Reference solution. Dissolve 66.6 mg of *miltefosine IPRS* in the solvent mixture with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture. Dilute a suitable volume of the solution with solvent mixture to obtain a solution having a similar concentration to that of the test solution.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm) (Such as Xbridge 18),
- column temperature: 40˚,
- sample temperature: 15º,
- mobile phase: a mixture of 20 volumes of a buffer solution prepared by dissolving 1.36 g of *sodium acetate trihydrate* in 1000 ml of *water*, adjusted to pH 3.0 with 10 per cent v/v of *trifluoroacetic acid*, 60 volumes of *acetonitrile* and 20 volumes of *methanol*.
- flow rate: 1 ml per minute,
- refractometer detector, maintained at 35˚,
- injection volume: 100 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 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 $C_{21}H_{46}NO_4P$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_{21}H_{46}NO_4P$.

Related substances. Determine by liquid chromatography (2.4.14),

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

Test solution. Disperse a quantity of the mixed content of the capsulescontaining 0.5 g of Miltefosine in the solvent mixture, with the aid of ultrasound for 15 minutes with intermittent shaking and dilute to 25.0 ml with the solvent mixture, filter.

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

Chromatographic system
- a stainless steel column 50 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (2.7 µm) (Such as Poroshell 120 EC-C-18),
- column temperature: 45˚,
- sample temperature: 10º,
- mobile phase: a mixture of 45 volumes of a buffer solution prepared by dissolving 1.36 g of *sodium acetate trihydrate* in 1000 ml of *water*, adjusted to pH 3.5 with 10 per cent v/v of *trifluoroacetic acid*, 35 volumes of *acetonitrile* and 25 volumes of *methanol*.
- flow rate: 0.9 ml per minute,
- refractometer detector, maintained at 45˚,
- injection volume: 100 µl.

Name	Relative retention time
Miltefosine impurity A [1*]	0.20
Miltefosine impurity B [2*]	0.47
Miltefosine impurity C[3*]	0.74
Miltefosine (Retention time: about 30 minutes)	1.0
Miltefosine impurity D[4*]	1.46
Miltefosine impurity E[5*]	2.09
Miltefosine impurity G[6*]	3.46

[*]Process impurity included for information only, not to be included in total degradation product.
[1]dodecyl(2-(trimethylammonio)ethyl)phosphate.
[2] tetradecyl(2-(trimethylammonio)ethyl)phosphate.
[3]pentadecyl(2-(trimethylammonio)ethyl)phosphate.
[4]2-aminoethyl hexadecyl hydrogen phosphate.
[5]heptadecyl(2-(trimethylammonio)ethyl)phosphate.
[6]hexadecyl dihydrogen phosphate.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates and the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent).

Microbial contamination (2.2.9). Total aerobic viable count is not more than 2000 cfu per g and total fungal count not more than 200 cfu per g. 1g is free from *Escherichia coli*.

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14).

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

Test solution. Weigh and mix the content of 20 capsules. Disperse a quantity of the mixed content containing 100 mg of Miltefosine in the solvent mixture with the aid of ultrasound for 35 minutes with intermittent shaking and dilute to 100.0 ml with the solvent mixture, Centrifuge a portion of the solution at 7000 rpm for 10 minutes. Use the clear supernatant liquid.

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

Use the chromatographic system as described under Dissolution with the following modification.

– injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 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 $C_{21}H_{46}NO_4P$ in the capsules.

Storage. Store at a temperature not exceeding 30°.