Technical Specification of Amphotericin-B for injection for Kala Azar under NVBDCP

08/8/2012

Amphotericin-B for injection should comply with the standard given in IP.

Amphotericin-B for injection is a sterile freeze dried mixture of Amphotericin-B and dexycholate sodium with one or more buffering agents. It is filled in a sealed container.

The injection is constituted by dissolving and contents of the sealed container in the requisite amount of sterile Water for injection, 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.

Amphotericin-B injection contains not less than 90.0 percent and not more than 120.0 per cent of the stated amount of Amphotericin-B $C_{47}H_{73}NO_{17}$.

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

Usual Strength:

50 mg per ml.

Tests:

pH (2.4.24).7.2 to 8.0 determined in a solution containing 10 mg per ml of Amphotericin B.

Bacterial Endotoxins (2.2.3)

Not more than 5.0 Endotoxin unit per mg of Amphotericin B for products used or labelled for intrathecal injection, not more than 0.9 Endotoxin unit per mg.

Loss on drying (2.4.19)

Not more than 8.0 per cent, determined on 0.1 g by drying in an oven at 60° at a pressure not exceeding 0.7 kPa.

Assay:

Determine by the microbiological assay of antibiotics, Method A (2.2.10) on a solution prepared in the following manner.

Mix the contents of 10 containers, dissolve in dimethylformamide. Express the results in mg per vial, taking each 1000 units found to be equivalent to 1 mg of Amphotericin-B.

Storage:

Store in tightly closed container between 2° to 8°, protected from light.

Labeling:

Label it to state that it is intended for use by intravenous infusion to hospitalized patients only, and that the solution be protected from light during administration.

Shelf-life: 24 months

At least 3/4th of the shelf life must remain at the time of delivery to the consignee. The supplier will provide manufacturer's stability test data substantiating the claimed shelf life in the offered package.

Labelling:

The label on each ampoule shall conform to the requirements of Rule 96 of Drugs & Cosmetics Act and Indian Pharmacopoeia and shall appear in the language of English.

All labelling should be in weatherproof ink and shall withstand immersion in water and remain intact. In addition, all labels shall state the name of the manufacturer, manufacturing license number, address of manufacturer, lot number, and expiry date. The label should bear a statement "the preparation is intended for intravenous injection only"

Labelling for secondary packaging:

A label must be affixed either on the top and/or front surface of the secondary package. It should indicate the number of ampoules, the name of the manufacturer, batch number, date of manufacture, date of expiry, and storage conditions. The label should bear a statement "the preparation is intended for intravenous injection only".

Additional Labelling:

All the containers and other outer containers shall be marked with the statement **"NVBDCP SUPPLY NOT FOR SALE"** in English. All labels on containers i.e. vials, cartons etc. should be marked with the statement **"NVBDCP SUPPLY NOT FOR SALE"** in bold red letters in English.

Printed Material:

Information sheets, printed in English, shall be included in each secondary package and shall include information, such as, administration, adverse effects, contraindications, precautions and storage conditions.

Quality Assurance:

Compliance:

The Supplier shall guarantee that the products as packed for shipment (a) comply with all provisions of the specification and related documents; (b) meet the recognized standards for safety, efficacy and quality; (c) are fit for the purposes made known to the Seller (d) are free from defects in workmanship and in materials and (e) the product has been manufactured as per WHO-GMP requirements.

Evidence:

The Supplier shall provide objective evidence, acceptable to the Purchaser, of the satisfaction of the requirements of this document for which no specific inspection has been mentioned.

The Supplier shall provide a copy of the Certificate of Analysis for each lot intended for shipment. The Supplier shall provide to the Purchaser a copy of the approval of each source material, constituent material and component for each lot intended for shipment. The test data for raw materials including glass container, in-process, finished product and packaging material testing must be on record for each lot shipped and must be made available to Purchaser's representatives when requested.

Packing:

Primary Package:

IP Type 1 amber coloured glass vial provided with compatible elastomer closure and crimp-on aluminium seal and plastic overcap. Each vial shall contain 50 mg of Amphotericin B for injection. Sufficient overages are added as per Pharmacopoeia so that 50 mg of extractable quantity can be achieved.

Secondary Package:

15 vials should be packed suitably segregated from each other by providing honeycomb box/ cardboard trays/polymer trays partitioning with proper cushioning in boxes for easy handling, transport and distribution. The box may contain 15 vials. It shall be fabricated from Millboard/ grey board/ cardboard with a minimum of bursting strength of 400gsm.

Sterile Water for Injections:

Description:

A clear colourless solution, odourless free from added substances.

Each ampoule shall contain 05 ml of Sterile Water of Injection.

The quality of Sterile Water for Injection should conform to the requirements of IP. If not mentioned in IP then other Pharmacopoeia of equivalent accuracy in case of international transactions may be followed.

Storage:

Store in a single dose container.

Shelf-life:

At least $5/6^{th}$ of the shelf life must remain at the time of delivery to the consignee. The supplier will provide manufacturer's stability test data substantiating the claimed shelf life in the proposed package.

Labelling:

The label on each ampoule shall conform to the requirements of Rule 96 of Drugs & Cosmetics Act and IP and shall appear in the language of English/Hindi.

All labelling should be in weatherproof ink and shall withstand immersion in water and remain intact. In addition to the requirements given in IP, all labels shall state the name of the manufacturer, manufacturing license number, address of manufacturer, lot number and expiry date.

Labelling for secondary packaging:

A label must be affixed either on the top and/or front surface of the secondary package. It should indicate the number of vials, the name of the manufacturer, batch number, date of manufacture, date of expiry and storage conditions.

Quality Assurance:

Compliance:

The Supplier shall guarantee that the products as packed for shipment (a) comply with all provisions of the specification and related documents; (b) meet the recognized standards for safety, efficacy and quality; (c) are fit for the purposes made known to the Seller (d) are free from defects in workmanship and in materials and (e) the product has been manufactured as per GMP included in Schedule M. In case of International transaction WHO GMP requirements shall be applicable.

Evidence:

The Supplier shall provide objective evidence, acceptable to the Purchaser, of the satisfaction of the requirements of this document for which no specific inspection has been mentioned.

The Supplier shall provide a copy of the manufacturing record and procedures to the Purchaser for each lot intended for shipment.

The Supplier shall provide a copy of the Certificate of Analysis for each lot intended for shipment.

The test data for raw materials including water for injection, glass container, in-process, finished product and packaging material testing must be on record for each lot shipped and must be made available to Purchaser's representatives when requested.

Details of samples lifted for testing (such as Millboard/Greyboard boxes, batch no. etc;) should be pasted on the packing of 5 Ply Shipper and records to this effect to be made available to the purchaser

Packing:

Primary Package:

IP Type 1 clear plain glass ampoules or PE ampoule based on FFS technology. Each ampoule shall contain 05 ml of sterile water for injection. The ampoule should be sufficiently transparent to permit visual inspection of the contents.

Secondary Package:

The ampoules should be packed suitably segregated from each other by providing honeycomb /cardboard trays/polymer trays with proper cushioning. It shall be fabricated from Millboard/ grey board/ cardboard with a minimum of bursting strength of 400gsm. The box should contain 15 Sterile Water for Injections.

Disposable Syringe and Disposable Needle:

Description (Disposable Syringe):

Disposable Syringes are Sterile Hypodermic Syringes for Single Use and are fabricated from virgin plastic. They shall conform to the standards given in IS 10258:2002. These are medical device intended for immediate use for administration of injectable preparations. They are supplied sterile and pyrogen – free and not to be re-sterilised or reused.

All labeling should be in weatherproof ink and shall withstand immersion in water and remain intact. In addition to the requirements given in Drugs & Cosmetic Act 1940 and rules there under, following information should be available:

- A description of the syringe including the capacity/ A description of the Needle Including the Gauge and the nominal length
- The word 'Sterile'
- That the syringe/needle is for single use only
- A solvent incompatibility
- The batch number
- Name and address of the manufacturer
- Date of Manufacture and Date of Expiry
- Warning that the syringe is not to be used if the packaging is damaged or sterility protector is loose
- CE marking
- ISO symbol for "do not re-use"

Labelling for secondary packaging:

Secondary Package:

A label must be affixed either on the top and/or front surface of the secondary package. It should indicate:

- A description of the syringe including the capacity and the type of nozzle/ A description of the needle including the gauze and the nominal length
- Quantity of primary packages
- The word 'Sterile'
- That the syringe is for single use only
- The batch number
- The date (month and year) of sterilization
- Name and address of the manufacturer
- Date of Manufacture and Date of Expiry
- Information for handling, storage and transportation

Quality Assurance:

Compliance:

The Supplier shall guarantee that the products as packed for shipment (a) comply with all provisions of the specification and related documents; (b) meet the recognized standards for safety, efficacy and quality; (c) are fit for the purposes made known to the Seller (d) are free from defects in workmanship and in materials and (e) the product has been manufactured as per GMP included in Schedule M - III. and (f) the product should conform to ISO 13485.

Evidence:

The Supplier shall provide objective evidence, acceptable to the Purchaser, of the satisfaction of the requirements of this document for which no specific inspection has been mentioned. The Supplier shall provide a copy of the manufacturing record and procedures to the Purchaser for each lot intended for shipment.

The Supplier shall provide documentary evidence that the sterilization of the syringes has been carried out by validated sterilization procedures (with appropriate controls and recording devices) in case it has been carried out in their premises. If the facility of other institution is used for sterilization, the approval of the licensing authority and documentary evidence for validated sterilization procedure should be made available.

The plastics and elastomer materials (polypropylene and polyethylene) of which the barrel and piston are made comply with the relevant specifications issued by BIS. The Syringes comply with the following standards regarding Dimensions including dead volume.

Capacity of the Syringe ml	Tolerance eq. or ex. to cap.	Tolerance < half of cap.	Max. Dead Vol. ml	Length of long Gradu-ation Mark, mm	Overall length of scale, mm	Scale Interval Ml	Increment. Between Graduation Lines ml
05	+_4% of expelled vol	+_1.5% nominal Cap, +1% of exp-elled vol	0.075	8	36	0.50	1

Polydimethylsiloxane (Silicone Oil) is applied to the internal walls of the barrel to assist in the smooth operation of the syringe but no excess be ensured capable of contaminating the contents at the time of use.

Description (Disposable Needles):

Sterile Hypodermic Needles for Single Use comprise of a length of hypodermic grade stainless steel tube connected to a hub that is designed to mate with a syringe or an IV set. They shall conform to the standards given in IS 10654:2002. The other end of the tube is sharpened at the tip as per IS requirements. The tube is covered with a shield made from polypropylene. The hub fabricated from poly propylene is colour coded as per the requirements of ISO 6009. The union of the hub and needle tube is carried out with epoxy adhesive. This medical device in conjunction with Syringe is intended for immediate use for administration of injectable preparations. They are supplied sterile and pyrogen – free and not to be re-sterilised or reused.

The Hypodermic needles shall comply with the following standards regarding Dimensions:

Needle Gauge	Colour of the hub	Nominal Length of the tube mm	Tolerance In length mm	Nominal outside diameter of needle mm	Diameter of stylet for normal walled tubing mm
23	Blue	25	+ 1, -2	0.6	0.25

Storage:

Disposable Syringes and Disposable Needles should be stored in a clean, cool, dry and adequately ventilated place.

Shelf-life:

At least 5/6th of the shelf life must remain at the time of delivery to the consignee. The supplier will provide manufacturer's stability test data substantiating the claimed shelf life in the proposed package.

Labelling:

The label on each strip shall conform to the requirements of I.P and shall appear in the language of English/Hindi.

The supplier shall provide documentary evidence that the inks, glues and adhesives for the marking on the package and on the assembly of the syringe and its package (Wherever necessary) do not migrate across the walls.

The supplier shall provide documentary evidence in regards to bio-compatibility of the device as per the requirements given in "Biological Evaluation of Medical Devices" IS 12572.

The supplier shall provide a copy of CE certificate.

The Supplier shall provide a copy of the Certificate of Analysis for each lot intended for shipment.

The test data for raw materials, in-process, finished product and packaging material testing must be on record for each lot shipped and must be made available to Purchaser's representatives when requested.

A. Packing:

Primary Package:

Each syringe and needle shall be packed and sealed separately in a primary container. The material of each container should not have detrimental effects on the contents. The material and design should be such as to ensure:

a) The maintenance of sterility under dry, clean and adequately ventilated storage conditions;
b) The minimum risk of contamination of the contents during opening of the container and removal of the contents;
c) Adequate protection of the contents during normal handling, transit and storage;
d) That once opened, the container cannot be easily resealed, and it should be obvious that the container has been opened.
e) Paper-PVC Blister:
f) PVC Film: Transparent, clear, food grade, blister forming PVC film, film gauge- 200 microns, PE coating: 25 microns.
g) Hard tempered Blister paper, VMCH coated, Thickness: 0.025mm

Secondary Package:

The primary package should be packed in boxes for easy handling, transport and distribution. The box may contain 15 primary packages. It shall be fabricated from Millboard/ grey board/ cardboard with a minimum of bursting strength of 400gsm.

B. Inspection:

The Purchaser may inspect and sample, or cause to be sampled, the product at the Supplier's factory and/or warehouse at a mutually agreeable time prior to the shipment of the product. Details of samples lifted for testing (such as Millboard/Greyboard boxes, batch no. etc;) should be pasted on the packing of 5 Ply Shipper and records to this effect to be made available to the purchaser

C. Testing:

The Purchaser may cause independent laboratory testing to be performed as deemed necessary to assure that the goods conform to the prescribed requirements. The said laboratory testing shall be of the Purchaser's choice if suitably equipped and qualified to conduct quality assurance tests on the product.

D. Labelling on Shipper Package:

The external surface of insulated packages should be either white or in the natural color of corrugated carton.

The labels on tertiary packaging must be attached to at least two sides. The label should include the name of the product, the number of secondary package (boxes) of Amphotericin-B Injections and Disposable Syringes plus Disposable Needles, the name of the manufacturer, Master batch number, date of manufacture, and date of expiry.

The label shall include bar code and be tear proof to be pasted on smooth surface to enable it to be read by bar code reader.

E. Packing for Shipper Package:

The boxes shall be packed in weather resistant triple walled insulated corrugated 5-ply cartons, each ply having strength of minimum 150 gsm. It should be fabricated from virgin quality 'A' grade material. The overall dimension of the carton should be such that the product does not get damaged during transportation and storage. Each Shipper Package shall contain 50 secondary packs of Amphotericin-B for injection, 50 secondary packs of Sterile Water for Injections & 50 secondary packs of Disposable Syringe and Disposable Needle.

F. Qualification of the Manufacturer:

The Bidder shall furnish a certificate from the competent Regulatory Authority that the manufacturer of the pharmaceutical product is licensed to manufacture these products. The manufacturing facility must conform to WHO-GMP standards. In case of medical devices the manufacturing facility must conform to the standards given in Schedule M-III of Drugs & Cosmetics Act and ISO 13485.

G. Recalls:

If products must be recalled because of problems with product quality or adverse reactions to the drug, the Supplier will be obliged to notify the purchaser providing full details about the reason leading to the recall and shall take steps to replace the product in question at its own cost with a fresh batch of acceptable quality, or withdraw and give a full refund if the product has been taken off the market due to safety problems.

H. Colour Coding:

The labels on secondary packing, tertiary and shipper package shall be identified by WHITE background.

I. Bar Coding:

Bar code shall be used to track down the product. It shall be printed on the label of Shipper containing

1) Product identification (GTIN 14) using application identifier (01)
2) Expiry Date in YYMMDD format & using application identifier (17)
3) Master batch number using application identifier (10)

Complete details on GS1 standards along with technical guidelines can be downloaded from www.gs 1india.org or www.gs1.org

J. Markings:

All containers and invoices must bear the name of the product, expiry dates of and appropriate storage conditions.

Inner boxes:

The inner boxes shall be marked with the following information in a clearly legible manner which is acceptable to the Purchaser:

- Generic name of the product
- Strength in terms of active ingredient in mg per ml wherever required
- Names and concentrations of the adjuvant/ preservative added wherever required
- Manufacturer's name and registered address
- Manufacturer's License number
- Lot or batch number
- Number of vials/ampoules/Syringes with needles contained in box
- Date of manufacture (month and year)
- Expiration date (month and year)
- Instructions for storage and handling
- Place of manufacture (Made in_____)

Exterior Shipping Cartons:

The following information shall be stenciled or labelled on the shipping cartons on all four sides in bold letters at least Ariel font size 14 with waterproof indelible ink in a clearly legible manner which is acceptable to the Purchaser:

- Generic name of the product
- Strength in terms of active ingredient in mg per ml
- Names and concentrations of the adjuvant/ preservative added
- Lot or batch number
- Date of manufacture (month and year)
- Expiration date (month and year)
- Manufacturer's name and registered address
- Manufacturer's national registration number
- Destination country license or registration number Consignee's address and emergency phone number including mobile number
- Destination airport
- Contract number
- Number of ampoules/Syringes-needles pouches/boxes contained in the carton
- Gross weight of each carton (in kg)
- Carton containing 50 secondary packages of each component.
- Instructions for storage and handling
- Place of manufacture (Made in_____)

K. Documentation:

Supplier shall provide to Purchaser a copy of the batch record, including all quality assurance documentation for the product being supplied.

Advance notice of arrival and advance shipping documentation:

Copies of the documentation for the goods to be shipped must be sent at least seven days in advance of arrival of the shipment. In the case of an individual contract for a specific destination that requires a longer period of advance notice, a longer period should apply.

The consignee(s) shall be intimated well in advance by registered letter/e-mail/ telephone, so that the products are collected from the airport immediately after arrival. The documentation must include the following:

- Pre-advice defined by the Purchaser;
- Airway bill (AWB);
- Supplier's invoice;
- Packing list;
- Lot release certificate (LRC) as per the requirements issued by the National Regulatory Authority (NRA) of the country of manufacture for each lot and
- Any other document, certificate or instruction specified in the individual order.

The documents shall be sent by e-mail and fax by the freight forwarder or the manufacturer to the consignee, the Purchaser, and any other parties specified in the individual contract.

The pre-advice must contain the following information:

- Purchase order reference;
- Consignee requisition reference;
- Number of packages and gross weight (in kilograms).
- Value of shipment (in Indian Rupees and US $);
- AWB and flight number(s);
- Date and time for place of departure, transit (if applicable), and arrival;
- Instructions for collection;
- Any other information specified in the individual contract must also be included for the consignee.

The following information shall be stated on the airway bill:

- Consignee's name, address, tel. number (including mobile no.) and e-mail ID.
- Purchase order reference;
- Consignee's requisition reference;
- Instructions to: "Telephone consignee upon arrival (repeat telephone number);

L. Dispatch:

Shipments should be scheduled to arrive outside weekends and/or public holidays in the recipient country and airline bookings should be made well ahead of the date of departure.

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