Product Permission Document (PPD) of Botulinum Toxin Type A for Injection Ph.Eur Purified Neurotoxin Complex

Brand Name : BOTO GENIE®

1. Introduction :

BOTO GENIE® (Botulinum Toxin Type A for Injection Ph.Eur) is produced from fermentation of *Clostridium botulinum* type A and purification of neurotoxin complex. It has unique pharmacological properties as neuromuscular blocking agent by inhibiting the released of acetylcholine resulting in partial, local, flaccid muscle paralysis, which helps to reduce some of the abnormal muscle contractions. The action of BOTO GENIE® (Botulinum Toxin Type A for Injection Ph.Eur) is reversible and can sustained partial chemical denervation for 3-6 months. Recovery of impulse transmission occurs gradually as new nerve terminal develops. One unit is defined as the median lethal intraperitoneal dose in mice estimated relative to the reference preparation assayed in parallel. The units of BOTO GENIE® are product specific and not applicable to other preparation, due to specific testing method such as vehicle dilution scheme, laboratory protocols and differences in species sensitivities.

1.1. Submission file :-

The Botulinum Toxin Type A for Injection Purified Ph. Eur. is licensed on license No. 08/SC/P of 2006 on form 28.

1.2. NDS Approval date and control :-

Permission given on Manufacturing license No. 08/SC/P of 2006 vide 20F/837/120 Dated 04/01/2007 and Drug/837/3866 dated 20/06/2012.

1.3. PPD –Biological revision date and control :-

PPD Biological Rev 01, Dated 01/07/2012.

1.4. Proprietary Name:-

BOTO GENIE®.

1.5. Non Proprietary name or common name of drug substance:-

Bulk purified toxin material of Botulinum Toxin Type A for Injection

1.6. Company Name :-

Bio-Med Private Limited
C-96 B.S. Road Industrial Area
Ghaziabad-201009, Uttar Pradesh India
Ph: 0091-120-4159857 / 4204862
Fax: 0120-4340219
E-mail: saryugarg@yahoo.com
Website: www.biomed.co.in

1.7. Name of Indian Distributer/Agent :-

Not Applicable as we are indigenous manufacturer of this product.

1.8. Therapeutic or Pharmacological classification :-

Injectables

1.9. Dosage form(s) :-

Lyophilized preparation with diluent for reconstitution.

1.10. Route of Administration:-

Subcutaneous/ Intramuscular/intradermal

1.11. Maximum Daily Dose :-

Not Applicable

S. Drug substance, name & manufacturer:-

S.1 Manufacturer (name, manufacturer) and address:-

Bio-Med Private Limited
C-96 B.S. Road Industrial Area
Ghaziabad-201009, Uttar Pradesh India
Ph: 0091-120-4159857 / 4204862
Fax: 0120-4340219
E-mail: saryugarg@yahoo.com
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S.1.1 Manufacturer(s) (name, manufacturer):-

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S.1.2. Description of manufacturing process & process control:-

Manufacturing Process	Controls
Strain of *Clostridium Botulinum* Toxin Type A	Record of history and characterization
Seed propagation and establishment of mother seed lot (freeze dried). Stored at or below -20^{o}C. Passage level – P-0.	Control of bacterial purity by morphological, biochemical and Immunological tests and *in-vivo* tests.
Seed propagation and establishment of working seed lot (freeze dried). Stored at or below -20^{o}C. Passage level – P-1	Control of bacterial purity by morphological, biochemical and immunological tests and *in-vivo* tests.
Revival and propagation of pre-cultures from working seed lot. (50 ml, 500 ml)	Bacterial purity, identification by microscopic examination of Gram's stained smears (at least 10,000 organisms are inspected), motility test.
Production of single harvest (5000 ml) passage level P-4	• Culture media sterility • pH control • Temperature control • Control of bacterial purity By microscopic examination of Gram's stained smears (at least 10,000 organisms are inspected), motility test, inoculation into solid media.
Bacterial cell separation by filtration by 0.2micron membrane capsule filter	• Control of filter integrity. • Sterility test
Purification of Botulinum Toxin Type A by • Culture acid precipitation • Washed acid precipitation • Calcium chloride extraction • Second acid precipitation • Alcohol precipitation • Crystallization of toxin by ammonium sulfate	• Control of centrifugation speed. • Temperature control • Control of pH
Sterile filtration of purified bulk material by 0.2-micron membrane capsule filter. Purified bulk material stored at or below –20^{0}C	• Residual Reagent & Nucleic Acid Removal • Immunological Identity • Specific Activity • Protein Test • Protein Profile • Sterility test

S.1.3. Control of materials:-

As in point No. S.1.2

S.1.4 Controls of critical steps and intermediate:-

As in point No. S.1.2

S.2. Characterization of drug substance

S.2.1 Elucidation of structure and other characteristics :-

Bulk purified toxin lot of Botulinum Toxin Type A For Injection is characterized as per the guidelines of European Pharmacopoeia.

General Properties :

Analytical testing performed to characterize the Bulk purified toxin lot of Botulinum Toxin Type A For Injection are follows:-

- Residual Reagent & Nucleic Acid Removal
- Immunological Identity
- Specific Activity
- Protein Test
- Protein Profile
- Sterility test

S.2.1.1 Physiochemical property:-

Analytical testing performed to characterize the Bulk purified toxin lot of Botulinum Toxin Type A For Injection are follows:-

- Residual Reagent & Nucleic Acid Removal
- Protein Test
- Protein Profile

S.2.1.2 Biological Characterization

- Bulk purified toxin material lot of Botulinum Toxin Type A for Injection is tested for Specific Activity, Immunological Identity and sterility by direct inoculation method

S.2.2 Impurities :-

Bulk purified toxin material lot of Botulinum Toxin Type A for Injection have been characterized for Residual reagent, Nucleic acid and Protein content.

S.3. Control of drug substance

S.3.1. Specification:-

S. No	Test Performed	Specifications as per European Pharmacopoeia
1.	Residual Reagent & Nucleic Acid Removal	UV ratio 260/280 shall be less than or equal to 1.0.
2.	Immunological Identity	The presence of a precipitin line between the corresponding wells indicate the presence of the antigen or the antibody in the sample and vice-versa.
3.	Specific Activity	Specific activity must not be less than $1x10^7$ mouse LD_{50} unit per milligram of protein for the 900000 relative molecular mass neurotoxin.
4.	Protein Test	Each lot of bulk purified toxin material of Botulinum toxin type A for Injection shall contain not less than 10^7 units per milligram of protein, as determined by Lowery et. al. method using bovine plasma albumin as a reference.
5.	Protein Profile	The native gel exhibit single major band ascertaining homogeneous toxin complex and purity.
6.	Sterility test	No evidenced of microbial growth is observed in any of the inoculated bottles than the preparation being examined complies with the test for sterility.

S.3.2. Stability:-

Stability study at real time (at or below -20°C) and accelerated condition (2-8°C) was carried out on three lots of purified toxin material (bulk) of Botulinum Toxin Type A For Injection. The conditions of study and number of batches considered are satisfactory.

From the result of stability study it was concluded that the drug substance was found to be stable in real time (at or below -20°C) and accelerated condition (2-8°C). Hence, shelf life of 5 years was assigned for the product under recommended storage conditions (at or below -20°C).

P. Drug product (name, Dosage form) :-

P.1. Manufacturer (name, Dosage form):-

P.1.1. Manufacturer(s) (name, dosage form):-

Bio-Med Private Limited
C-96 B.S. Road Industrial Area
Ghaziabad-201009, Uttar Pradesh India
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Website:www.biomed.co.in

P.1.2. Batch formula:-

COMPOSITION :-

(A) BOTO GENIE® 100 Units Vial (Freeze Dried)
Botulinum Toxin Type A.....100 unit
Purified Neurotoxin Complex
Lactose (stabilizer).....5 mg

(B) BOTO GENIE® 50 Units Vial (Freeze Dried)
Botulinum Toxin Type A.....50 unit
Purified Neurotoxin Complex
Lactose (stabilizer).....5 mg

(C) DILUENT
Sodium Chloride Injection I.P.

P.1.3. Description of Manufacturing process & process control

The final bulk of Botulinum Toxin Type A For Injection is prepared by aseptic dilution of the purified toxin lot based on the toxin concentration. The dilution of the purified toxin lot for the preparation of final bulk is done by adding stabilizer (Lactose).

The final lot is prepared by aseptically dispensing the final bulk injection, in grade A conditions with grade B background, in tubular glass vials which have been final rinsed with water for injection and sterilized in dry heat sterilizer. During filling the volume of filling, room temperature, humidity, microbial load is periodically monitored.

Vials are half stoppered with butyl stoppers (pre-sterilized by radiation), collected and loaded into freeze drier. The lyophilization cycle have been validated and the moisture content of consecutive seven batches of final lot of Botulinum Toxin Type A For Injection meets the specifications of European Pharmacopoeia. After lyophilization cycle sterile nitrogen is introduced in the lyophilizer and vials are full stoppered. On removal from the lyophilizer the vials are sealed with aluminium caps. The sealed vials are visually inspected, labeled, packed and stored at 2-8^{o}C.

P.1.4. Control of critical steps & intermediate

Preparation of final bulk by aseptic dilution with water for injection and addition of lactose 5 mg/vial (Stabilizer)	• Temperature and humidity control • Sterility test
Containerization, stoppering, sealing, visual inspection, labeling, packing, and storage (2-8^{o}C) of final containers	• Volume control • Temperature control • Humidity control
Final lot of Botulinum Toxin Type A for Injection Ph. Eur.	• pH • Water • Identification • Sterility • Bacterial Endotoxins • Assay

P.2. Control of excipients:-

P.2.1.Excipients of Human or Animal Origin:

There is no use of excipient that is human or animal origin in the manufacturing of Botulinum Toxin Type A For Injection Ph.Eur.

P.3. Control of Drug Product:-

P.3.1. Specification (s):

S. No	Test Performed	Specifications as per European Pharmacopoeia
1	pH	The pH of the reconstituted product is within 6.8 ± 0.5.
2	Water	Not more than 3 %
3	Identification	The presence of Botulinum Toxin Type A confirmed by immunochemical method.
4	Sterility	No evidence of microbial growth is observed in any of the inoculated bottles than the preparation being examined complies with the test for sterility.
5	Bacterial Endotoxins	Less than 10 IU per vial.
6	Assay	LD_{50} in mice, relative to reference preparation. The estimated potency is not less than 80% and not more than 125% of the stated potency. The confidence limits (P=0.95) are not less than 80% and not more than 125% of the estimated potency. The test may be repeated but when more than 1 test is performed, the results of all valid tests must be combined in the estimate of potency.

P.3.2. Container Closure System (name, dosage form):

Various material used for the final packing of Botulinum Toxin Type A For Injection Ph.Eur are as follows:

For 50 units	For 100 units
Glass Vials :- 5 ml, 20 mm USP Type -I clear tubular glass vial. Rubber closures :- 20mm Grey Slotted Rubber stopper. Aluminium Seals :- 20 mm flip off aluminium seals blue (BE-11)	Glass Vials :- 5 ml, 20 mm USP Type -I clear tubular glass vial. Rubber closures :- 20mm Grey Slotted Rubber stopper. Aluminium Seals :- 13mm flip off aluminium seals pink (PK-1)

P.4. Stability:-

P.4.1 Stability Summary and Conclusion:-

Stability studies real time (2-8^{o}C) and at accelerated condition (20-25^{o}C and 30-35^{o}C) have been conducted on three consecutive lots Botulinum Toxin Type a for Injection. The test results prove good stability of the product. Test specifications for release of final lot were met after storage at recommended storage condition (2-8^{o}C) for at least 48 months. Based on the results of stability studies shelf life of 36 months was assigned for final lot of at recommended storage condition of +2 to +8^{o}C.

P.4.2 Post approval stability protocol and stability commitment (name, dosage form):

Every year one batch of BOTO GENIE® is subjected to real time stability study as per the approved protocol.

A. Appendices :- Refer module 3.2.A

A.1 Details of equipment and facilities for production of drug product

For Layout of the facility used for manufacturing of BOTO GENIE® and list of equipments refer to Module 3 Point No. 3.2.A.

A.2. Adventitious Agents Safety evaluation

For non-viral adventitious agents :-

The routine manufacturing control of adventitious agents, such as bacteria, mycoplasma and fungi, typically using well-established analytical procedure like sterility test.

Test for sterility is applied to pharmacopoeial articles that are required according to the pharmacopoeia to be sterile.

The test is designed to reveal the presence of micro-organisms in the sample used in the test; interpretation of the results of testing is based on the assumption that all units of an article or the entire bulk product or the contents of every container of the filled product in a lot or batch, had they been tested, would also have given the same results. Since all the units or the bulk or all the containers cannot be tested a sufficient number of samples of units or containers should be examined to give a suitable degree of confidence in the results of the tests.

Media used for the tests should comply with the growth promotion test. Fluid thioglycollate medium is primarily intended for the culture of anaerobic bacteria.
However, it will also detect aerobic bacteria, soyabean-casein digest medium is suitable for the culture of both fungi and aerobic bacteria.

For viral adventitious agents:-
Botulinum Toxin Type A for Injection is a freeze dried preparation therefore there is not found viral adventitious agents.

Materials of Biological Origin :-
There is no material of biological origin used in manufacturing of this product.