CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125360

CHEMISTRY REVIEW(S)

Review Cover Sheet

BLA STN 125360/0

Xeomin (NT-201)
(Botulinum Toxin Type A)

Merz Pharmaceuticals

Action date: July 30, 2010

Reviewer's Signatures:

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Indication:	Cervical Dystonia Blepharospasma
Labeled Strength:	50 and 100 Units/vial
(b) (4) (HSA):	Human Albumin, Sucrose

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I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125360 for Xeomin manufactured by Merz, Pharmaceuticals GMbH. The data submitted in this application support the conclusion that the manufacture of purified *C. botulinum* neurotoxin type A (BONT/A, uncomplexed) naturally secreted by *C. botulinum*, is well controlled, and leads to a product that is potent and safe, when used according to the label. The product is free from endogenous or adventitious infectious agents. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs.

The product was first registered for the treatment of blepharospasm and hemifacial spasm in the Germany in 2005. Since then, the product has been registered many counties for various indications (servical dystonia, blepharospasm, post-stroke upper limb spasticity and glabellar lines). The FDA safety group is currently assessing clinical experience from the clinical data generated from rest of the world.

This product will be on lot release per 21CFR 610. It is recommended that this product be approved for human use under the conditions specified in the package insert.

Recommendation on Phase 4 (Post-Marketing) Commitments and Agreements, if Approvable

CMC Post-Marketing Commitments

1. To characterize the specificity of the antibody used in the abnormal toxicity test to evaluate whether this antibody recognizes only type A toxin and not other serotypes. Results of this validation study together with the proposed specifications for use in drug product release and in the lot release protocol will be submitted in a Prior Approval Supplement (PAS) by [SPONSOR PROPOSE DATE].

2. To characterize the ability of the SE-HPLC assay to accurately assess the aggregate content of the drug substance at release and on stability. This may be established by demonstrating that SE-HPLC provides similar results in aggregate content evaluations as compared to an orthogonal method that is quantitative and does not disrupt weak protein- protein interactions (e.g., AUC or FFF). Results of this validation study will be submitted in a Prior Approval Supplement (PAS) by [SPONSOR PROPOSE DATE].

3. To investigate the development and implementation of a non-animal based potency assay for drug substance, drug product release and stability testing. A summary report together with any proposed modifications to the release and stability specifications should be submitted in a prior Approval Supplement to the Agency by [SPONSOR PROPOSE DATE].

II. Chemistry Executive Summary

A. Description of the Drug Product and Drug Substance

Structure

The active pharmaceutical ingredient of Xeomin is purified type A neurotoxin with a molecular weight of 150 kDa, free of complexed proteins, and produced by the anaerobic fermemtation of the bacterium *Clostridium botulinum,* Hall strain ATCC 3502. The neurotoxin moiety is a 1296 amino acid dichain molecule consisting of a heavy chain (Hc,100 kDa) and a light chain (Lc, 50 kDa) linked by a disulfide bond. The final product is a lyophilized material containing the type A toxin dichain, human albumin and sucrose.

Biological activity

Xeomin blocks neuromuscular transmission by binding to receptor sites on motor or sympathetic nerve terminals, entering the nerve terminal and inhibiting neurotransmitter (acetylcholine) release. The full activity of the toxin requires both the heavy (Hc) and light (Lc) chains. The Hc mediates neuron-specific binding, up-take by receptor-mediated endocytosis and transport of Lc across the endosomal membrane into the cytosol. In the cytosol the Lc, a zinc binding metallopeptidase, hydrolyzes a member of the SNARE protein complex, which is required for vesicle exocytosis. The Zn^{2+} binding sequence within each Lc, H-E-X-X-H, is a distinct minimal amino acid motif conserved within this toxin family.

The substrate for type A toxin is a 25-kD synaptosomal associated protein (SNAP-25). SNAP-25 is cleaved at the C-terminus (Q_{197}-R) by BoNT/A, generating truncated SNAP-25 that can't participate in formation of the SNARE core complex. When injected i.m. at therapeutic doses, Xeomin induces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. It is indicated for decreasing voluntary muscle power and improving abnormal head position, disability and neck pain in adult patients with severe cervical dystonia.

Potency Assays to Measure Activity

The mouse lethal dose assay is used to assess product activity. The assay is conducted by administration of pre-established dilutions of Xeomin into groups of mice. The number of deaths that occur at each dilution is measured over a fixed period of time. The concentration that leads to death in half of the test animals is the lethal dose 50 (LD_{50}). The potency of botulinum toxin therapeutic preparations is expressed in LD_{50} units, with one unit of activity defined as the amount of drug required to kill 50% of the animals. The assay is a good indicator of both light and heavy chain function since both are

required for activity *in vivo*. A major drawback of this assay is that it is much more variable than cell based assays, requiring sacrifice of hundreds of mice for each potency activity measurement. Moreover, there is huge inter-laboratory variability, precluding standardization of LD50 units between products. Currently a reliable *in vitro* non-animal based assay to replace the mLD50 test is not available. Therefore the mLD50 assay is still used to assess potency for release of all botulinum toxin products currently on the market in the US and Europe.

Drug Product Presentation

Xeomin is supplied as a sterile single use vial. Each 100 or 50 Unit vial contains lyophylized *C.botulinum* toxin type A, sucrose (4.7 mg) and human albumin (1 mg). The DP is packaged in 3 ml Type I clear (b) (4) glass vials with (b) (4) rubber closure and sealed with 13 mm (b) (4) flip top overseals. As each vial is for single patient use, no anti-microbial preservatives are included in the formulation.

Excipients

The product is formulated with sucrose and human albumin. Sucrose, a natural disaccharide obtained from plants is a common pharmaceutical excipient used in oral, parenteral and inhalational products and supplied by (b) (4) as a compendial product manufactured in accordance with the NF monograph. Human albumin is manufactured by CSL Behring and is a FDA approved medicinal product in the US (BLA-1-2366). Human plasma was received from selected donation centers in the US, authorized by FDA.

Drug Product Storage

Drug product is stored as a lyophile at 25°C. Drug product must be used within 24 h of reconstitution and should be stored at 2°C – 8°C. Drug product is photostable based on the results of testing conducted per ICH Q1b.

DS Manufacture:

(b) (4)

(b) (4) The process is validated and well-controlled through defined operating and performance parameters. The manufacturing site, Merz Group Services GmbH, Am Pharmpark 15A, D-06861 Dessau-Rosslau, Germany was inspected Nov 5 -13, 2009. A number of 483 observations were issued, none that preclude licensure at this time.

DS Purity

Xeomin DS is produced from bacterial fermentation. Since bacterial fermentation processes do not support the growth of mammalian viruses the purification process is not required to include viral clearance steps or the examination of viral particles in the product. Drug substance is highly pure and does not contain process-related impurities.

DS Release Tests

The tests for release of DS include the following: appearance (b) (4); protein content (b) (4) ELISA and SE-HPLC); immunological identity (Western blot for HC and LC, ELISA for presence of BoNT/A, reduced SDS-PAGE identity: single chain, HC and LD), reduced SDS-PAGE); purity and product related impurities (Coomassie stain); bioburden (b) (4)); endotoxin (b) (4), and aggregates (SE-HPLC (b) (4) aggregates). Drug product is formulated with an excess of HSA and DS is present in nanogram quantities. Therefore it is not possible to test DP for aggregates. Since the presence of aggregates can promote immunogenicity this is a safety concern, albeit a limited one because the drug is administered intramuscularly at low dose and is highly diluted.

Development and Comparability

The drug substance manufacturing process was originally developed at (b) (4), (b) (4) Subsequently, the process was transferred to a dedicated Merz Pharm (MP) production facility in Dessau-Rosslau, Germany.

During clinical development for cervical dystonia and blepharospasm, drug substance used for formulation of clinical trial drug product was changed from the (b) (4), material to the MP material. There are no significant changes in the manufacturing process from (b) (4) to MP. The comparability of clinical material manufactured at (b) (4) and MP was established by physico-chemical and biological studies.

Stability

Loss of potency is observed when drug substance is stored at temperatures of 2-8 ^{0}C. Real time stability data indicate that drug substance is stable when stored frozen (-80 ^{0}C) for at least 36 months.

The proposed drug substance shelf life of 36 months when stored at -80 ^{0}C is supported by data submitted by the Sponsor.

B. Description of How the Drug Product is Intended to be Used

- Xeomin is a neuromuscular transmission blocking toxin indicated for decreasing voluntary muscle power and improving abnormal head position, disability and neck pain in adults with severe cervical dystonia. Xeomin is also indicated for a neurological movement disorder involving involuntary and sustained muscle contractions around the eyes and improving abnormal contraction or twitch of the eyelids in adults with benign essential blespharospasm. Xeomin is administered by intramuscular injection into a maximum of five clinically indicated muscles with a maximum total dose of (b) (4)s in a single session for

treating cervical dystonia. The total of dose of Xeomin is (b) (4) per eye per treatment session. It is into the clinically indicated muscles for blespharospasm. Recommended dose of Xeomin is (b) (4); intramuscularly every 3 months for dystonia and blespharospasma respectively.

- Each vial of Xeomin contains 100 units or 50 units of lyophilized *C. botulinum* toxin type A, 1 mg human albumin and 4.7 mg sucrose, free of preservatives.
- Xeomin is prepared for intramuscular injection by reconstituting each vial with 1 ml of 0.9% sodium chloride for injection USP.
- Xeomin vials can be stored at room temperature, in a refrigerator or freezer (- 20 ^{0}C, 5 ^{0}C or at + 25 ^{0}C). The increased stability of drug product relative to drug substance at higher temperatures is due to the stabilizing effects of the formulation excipients. The recommended expiration dating period for Xeomin is 36 months under these storage conditions.

C. Basis for Approvability or Not-Approval Recommendation

- Xeomin's manufacturing process is well-controlled and consistently delivers a quality product suitable for its intended use. Therefore based on a quality review it is approvable for the proposed indications.
- Post-marketing commitments described in the recommendations sections above will provide additional information to assure the continued safety and efficacy of the product.

Product Immunogenicity

Neutralizing anti-Xeomin antibody responses were measured using a hemidiaphragm assay. This assay assesses the ability of patient serum samples to inhibit the ability of Xeomin to prevent the ex-vivo contraction of mouse diaphragm muscles. No neutralizing antibodies were observed in patient sera. No loss of efficacy was observed in patients. This assay is sufficiently sensitive to detect low positive samples (3.25 mIU/ml or the amount of antibody needed to neutralize 32 U of drug).

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