

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125274

MICROBIOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: April 3, 2009
To: Administrative File, STN 125286/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT
Through: Kalavati Suvarna, Ph.D., Peer Reviewer, CDER/OC/DMPQ/BMT
Endorsement: Concepcion Cruz, Acting Branch Chief, CDER/OC/DMPQ/MAPCB
Subject: Team Leader Secondary Discipline Review
US License: 1787
Applicant: IPSEN Biopharm Limited
Facility: IPSEN Biopharm Limited, Wrexham, UK (FEI 1000346340)
Product: Reloxin® (*Clostridium botulinum* toxin Type A haemagglutinin complex, CNT-52120)
Dosage: Sterile lyophilized powder for Injection, 300 Units
Indication: Treatment of moderate to severe glabellar lines in adult patients
Due date: April 13, 2009

PSH 4/3/09
KSW 4/3/09
CC 4/3/09

Recommendation for Approvability:

Both Reloxin® (BLA 125286) and Dysport® (BLA 125274) are manufactured by Ipsen Biopharm Limited. However, Reloxin® is manufactured by Ipsen for Medicis Pharmaceutical Corporation. Medicis is responsible for the interpretation of the non-clinical and clinical contents of the BLA, including labeling. The Agency has communicated to Medicis on March 4, 2008 that only one license could be issued per product. Because two (2) BLAs were submitted to the Agency for the same product (but for different indications), once the first BLA is approved, the second application would be immediately and automatically be converted into a supplement to the licensed *Clostridium botulinum* type A toxin product.

A review of BLA 125274 (the first BLA submitted for the same product) was completed by OC/DMPQ/BMT on December 17, 2008. The CMC portion of BLA 125286 is the same as that described in BLA 125274 for Dysport (*Clostridium botulinum* toxin Type A haemagglutinin complex) from a sterility assurance and product quality microbiology perspective. BLA 125274 for Dysport® by Ipsen Biopharm Limited was reviewed by the Biotech Manufacturing Team reviewers Brenda Uratani, Ph.D. (CMC review dated December 11, 2008), Donald Obenhuber, Ph.D. (review dated December 11, 2008) and Patricia F.

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Hughes, Ph.D. (Team Leader review dated December 17, 2008). BLA 125274, as amended, was recommended for approval from a sterility assurance and microbiology product quality perspective.

The manufacturing facilities listed in BLA 125286 are the same as those listed in BLA 125274. A pre-license inspection of the Ipsen Biopharm Ltd. drug substance and drug product manufacturing facility in Wrexham LL13UF, UK was conducted in June 2008 by Michelle Clark-Stuart (OC/DMPQ/BMT) and Enan Guan (OBP/DTP) on June 2-10, 2008. No 483 observations were presented to the firm and the inspection was classified NAI.

Since the Microbiology CMC and manufacturing facilities sections of the BLA are the same for both Reloxin® and Dysport®, reference is made to BLA 125274 for the CMC review of BLA 125286 from a sterility assurance and microbiology product quality perspective for both drug substance and drug product. BLA 125286, as amended, is recommended for approval from a sterility assurance and microbiology product quality perspective.

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ON ORIGINAL**

cGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Ipsen Biopharm Ltd., Wrexham, UK was last inspected June 2-10, 2008 and classified NAI. The BTP profile was covered and is acceptable. Wickham Laboratories Ltd., Hampshire, UK was last inspected May 16-17, 2005 and classified VAI. The CTL profile was covered and is acceptable. There are no pending or ongoing compliance actions to prevent approval of BLA 125286 at this time.

Conclusion

- I. Cross reference is made to the CMC sections of BLA 125274 and to the CMC microbiology reviews conducted by Brenda Uratani and Donald Obenhuber of December 11, 2008 and Patricia F. Hughes of December 17, 2008 in support of BLA 125286. The drug substance and drug product sections of BLA 125286, including the manufacturing and testing facilities, are the same as those described in BLA 125274. BLA 125286, as amended, is recommended for approval from a sterility assurance and microbiology product quality perspective.
 - II. The drug substance and drug product sections not relating to microbiology quality issues should be assessed OBP/DTP reviewers.
 - III. A list of CGMP items to be followed up at the next surveillance inspection was included in the drug substance review memo from Brenda Uratani. These items will be communicated to the International Operations Group in Office of Regulatory Affairs by The Division of Manufacturing and Product Quality.
- Cc: WO Bldg 51, Uratani
WO Bldg 51, Obenhuber
WO Bldg 51, Hughes
WO Bldg 51, BMT Files (BLA 125286)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 11, 2008
To: Administrative File, STN 125274/0
From: Brenda Uratani, Ph.D., CDER/OC/DMPQ/BMT *for BU PFH 12/17/08*
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT *PFH 12/17/08*
Subject: Review of Biological License Application (BLA): new BLA
US License: 1787
Applicant: IPSEN Biopharm Limited
Facility: IPSEN Biopharm Limited, Wrexham, UK (FEI 1000346340)
Product: DYSPORT for Injection (*Clostridium botulinum* toxin Type A haemagglutinin complex)
Dosage: Sterile lyophilized powder (liquid) for intramuscular injection (300 U/vial and 500 U/vial)
Indication: Treatment of cervical dystonia
Due date: December 29, 2009

Recommendation: The drug substance section of the application, 2.3.S, was reviewed from a microbiological product quality perspective. The application, as amended, is recommended for approval.

Review Summary

IPSEN submitted this BLA in support of the manufacturing of *Clostridium botulinum* toxin Type A haemagglutinin complex bulk active substance (CNT52120 BAS), a 150 kDa polypeptide neurotoxin and a 120 kDa non-toxin haemagglutinin protein, and various smaller haemagglutinin proteins. The 150 kDa neurotoxin is initially produced as a single-chain protein which undergoes post-translational cleavage by endogenous proteases during fermentation into a fully active neurotoxin.

This drug is indicated for the treatment of cervical dystonia. Both the drug substance and drug product are manufactured at IPSEN Biopharm Ltd in Wrexham, UK.

The drug substance CMC sections of the BLA were evaluated in this review for adequacy from a microbiology product quality perspective. The sections evaluated include in part

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3.2.S.2, 3.2.S.4, 3.2.S.6, 3.2.S.7, and 3.2.A.1. The BLA was amended (number 28 on December 9, 2008) to address deficiencies identified during the review of the BLA.

A pre-approval inspection of IPSEN Biopharm manufacturing facility was conducted by BMT (Michelle Clark Stuart), and OBP/DTP on June 02-10, 2008- NAI no 483 observations.

Drug Substance

Manufacturer-3.2.S.2

Table 3.2.S.2.1-1 Sites and Activities for the Manufacture and Testing of the CNT52120 Bulk Active Substance

Name and Address of Site	Activities Occurring at Site
IPSEN Biopharm Ltd. Wrexham Industrial Estate Ash Road Wrexham LL13 9UF UK Tel: +44 (0)1978 661181	<ul style="list-style-type: none">• Manufacture of CNT52120 BAS• Raw material testing and release• In-process testing during the manufacture of CNT52120 BAS• Environmental monitoring• CNT52120 BAS release testing• CNT52120 BAS stability testing••••

b(4)

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X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Environmental Assessment

Ipsen requests a categorical exclusion from providing an environmental assessment for the commercial manufacture, distribution and use of DYSPORT for Injection." The BLA states the following:

"Dysport® for Injection (*Clostridium botulinum* type A hemagglutinin complex) is a biologic product manufactured from clostridium botulinum toxin type A, which occurs naturally in the environment.For the treatment of this rare disease, Dysport is administered by a small, local, injection in the affected muscle(s) once every 12-16 weeks or longer. Moreover, to the Applicant's knowledge, no extraordinary circumstances exist that would warrant an environmental assessment [21 CFR Part 25.31(d)]. Therefore, given the rarity of the disease, it's localized administration, and the infrequent use of the product, the Agency's approval of Dysport is not expected to significantly alter the concentration or distribution of clostridium botulinum toxin type A, its metabolites, or degradation products in the environment. Consequently, a categorical exclusion for an Environmental Analysis, as stated in 21 CFR Part 25.31 (c), is requested."

cGMP Status

"The Manufacturing Assessment and Preapproval Compliance Branch has completed the review and evaluation of the TB-EER below. The June 2008 inspection conducted by Michelle Clark-Stuart on June 2-10, 2008 has been classified NAI by the International Compliance Team. There are no pending or ongoing compliance actions or investigations to prevent approval of STN 125274 at this time."

Conclusion

- I. The drug substance section of the application is adequate from a microbiology product quality perspective.
- II. The drug substance control of Source and Starting Materials of Biological Origin, Generation of Cell Substrate, Cell banking System, Characterization, Batch Analyses, Justification of Specifications, Reference Standards, and Stability sections are reviewed by OBP/DMA.
- III. Additional inspectional follow-up items include:
 - Evaluate methodology, sensitivity of the bioburden test, and trending data.
 - Evaluate endotoxin controls.
 - Evaluate the adequacy of room classification, pressure differentials, and EM trending.
 - Evaluate the type of BI used in sterilization validation of equipment since the D value of *C. botulinum* can be as high as 3 minutes. Has the firm made proper evaluation of the BI suitable for sterilization validation?

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- Evaluated bacterial endotoxin test used for bulk drug substance release.

Cc: WO Bldg 51, Uratani
WO Bldg 51, Hughes
WO Bldg 51, Friedman
WO Bldg 51, BMT Files (BLA 125274)

Archived File: S:\archive\BLA\125274\125274.rev.mem.BLA.DS.12-11-08.doc

**APPEARS THIS WAY
ON ORIGINAL**



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: December 11, 2008
To: Administrative File, STN 125274
From: Donald Obenhuber, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *Dec 12/17/08*
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT *Pat 12/17/08*
Edwin Rivera, Branch Chief, CDER/OC/DMPQ/MAPCB *Edw 12/17/08*
Subject: Review of BLA for the treatment of cervical dystonia (spasmodic torticollis)
US License: 1787
Applicant: Ipsen Biopharm Limited
Facility: Ipsen Biopharm, Limited Wrexham LL13 9UF, UK, FEI=1000346340
Product: Dysport® for Injection (Clostridium Botulinum Toxin Type A Hemagglutinin Complex)
Dosage: 300 U/vial or 500 U/vial (sterile lyophilized power); in single use 3ml stoppered glass vials with flip top seals is to be reconstituted with 1 mL of 0.9% Sodium Chloride Injection USP (without preservative) intended for intramuscular injection.
Indication: Treatment of cervical dystonia (spasmodic torticollis)
Due date: 28 December 2008

RECOMMENDATION ON APPROVABILITY: The submission, as amended, is recommended for approval on the basis of sterility assurance. All deficiencies identified (deficiencies are listed on page 27-29 of this review) during the assessment of this BLA were adequately addressed by the sponsor and the BLA was appropriately amended.

The following amendments were submitted in response to microbiology product quality deficiencies identified during the review of the BLA.

- Amendment 18, September 18, 2008
- Amendment 19, September 19, 2008
- Amendment 27, December 3, 2008
- Amendment 28, December 9, 2008

PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

MANUFACTURING PROCESS

b(4)

CNT52120 Bulk Active Substance (BAS) Clostridium botulinum toxin Type A haemagglutinin complex is manufactured using the following chemical components (3.2.P.1):

Ingredients	Vial Content	
	300 U/vial	500 U/vial
CNT52120 (Lyophilized)		
Albumin Human		125 ug
Lactose monohydrate		2.5 mg

The following represents the components comprising the container/closure systems. Drug Product is supplied in neutral 3 mL glass vials, sealed with 13 mm rubber closures and oversealed with 13 mm flip top seals. The color of the flip off top on the seal is unique to the CNT52120 Drug Product concentration.

b(4)

Container Closure Component	Manufacturer/ Supplier/ Address	Description of the Component	Material of Construction Pharmacopoeia Compliance	DMF No.
Glass vial				
Closure				
Flip top overseal				

b(4)

The following summarizes the batch composition

26 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Container Closure Integrity

Please provide stability data for Container Closure Integrity testing.

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