

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761225Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: February 9, 2024

To: H.F. Van Horn, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Tong Li-Masters, MD, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for LETYBO (letibotulinumtoxinA-wlbq) for injection, for intramuscular use

BLA: 761225

Background:

In response to DDD's consult request dated October 2, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA submission for LETYBO.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 30, 2024, and our comments are provided below/we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on February 2, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on January 30, 2024, and our comments are below.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
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MEMORANDUM
REVIEW OF REVISED LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 6, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761225
Product Name, Dosage Form, and Strength:	Letybo (letibotulinumtoxinA-wlb ^a) for injection, 50 units/vial and 100 units/vial
Applicant/Sponsor Name:	Hugel, Inc.
TTT ID #:	2022-2294-2
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on January 30, 2024 for Letybo. The Division of Dermatology and Dentistry (DDD) requested that we review the revised carton labeling for Letybo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder letibotulinumtoxinA-wlb^a is used throughout this review to refer to the non-proprietary name and suffix for this product.

^b Patel, M. Label and Labeling Review Memo for Letybo (BLA 761225). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 NOV 06. TTT ID No.: 2022-2294-1.

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/s/

MADHURI R PATEL
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YEVGENIYA M KOGAN
02/07/2024 12:22:51 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 2, 2024

To: H.F. Van Horn III, PharmD, MBA
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
David Foss, PharmD, MPH, BCPS, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): LETYBO (letibotulinumtoxinA-wlbq)

Dosage Form and Route: for injection, for intramuscular use

Application Type/Number: BLA 761225

Applicant: Hugel, Inc.

1 INTRODUCTION

On August 31, 2023, Hugel, Inc., submitted for the Agency's review a Class 2 Resubmission for their proposed Biologics License Application (BLA) 761225 for LETYBO (letibotulinumtoxinA-wlbq) for injection. The purpose of this resubmission is to address the deficiencies identified in the Complete Response (CR) letter issued by the Agency on April 12, 2023. The proposed indication for LETYBO (letibotulinumtoxinA-wlbq) for injection is for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on October 2, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for LETYBO (letibotulinumtoxinA-wlbq) for injection, for intramuscular use.

2 MATERIAL REVIEWED

- Draft LETYBO (letibotulinumtoxinA-wlbq) for injection MG received on August 31, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 30, 2024.
- Draft LETYBO (letibotulinumtoxinA-wlbq) for injection Prescribing Information (PI) received on August 31, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 30, 2024.
- DMPP-OPDP collaborative review of TRADENAME (letibotulinumtoxinA-xxxx) for injection MG dated February 1, 2023.
- Approved BOTOX/BOTOX Cosmetic (onabotulinumtoxinA), DYSPORT (abobotulinumtoxinA), XEOMIN (incobotulinumtoxinA), DAXXIFY (daxibotulinumtoxinA-lanm), and JEUVEAU (prabotulinumtoxinA-xvfs) comparator labeling dated August 11, 2023, September 21, 2023, September 8, 2023, August 11, 2023, and July 12, 2019 respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

RUTH I MAYROSH
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DAVID F FOSS
02/02/2024 09:48:09 AM

LASHAWN M GRIFFITHS
02/02/2024 09:55:08 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 6, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761225
Product Name, Dosage Form, and Strength:	Letybo (letibotulinumtoxinA-wlbg) ^a for injection, 50 units/vial and 100 units/vial
Applicant/Sponsor Name:	Hugel, Inc.
TTT ID #:	2022-2294-1
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

BLA 761225 received a Complete Response (CR) on April 12, 2023. We previously reviewed the labels and labeling and provided recommendations.^b This MEMO evaluates the revised container labels and carton labeling received on August 31, 2023 for Letybo. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Letybo (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective. The carton labeling is missing a linear barcode. Additionally, the 2D data matrix is located on a panel separate from the human-readable portion of the product identifier.

3 RECOMMENDATIONS FOR HUGEL, INC.

We recommend the following be implemented prior to approval of this BLA:

^a The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder letibotulinumtoxinA-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

^b Howard, C. Label and Labeling Review for Letybo (BLA 761225). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 20. TTT ID No.: 2022-2294.

A. Carton Labeling

- a. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.¹ We note the 2D data matrix is located on a panel separate from the human-readable portion of the product identifier. We continue to recommend that the human-readable portion be located near the 2D data matrix barcode.

NDC: [insert product' s NDC]

SERIAL: [insert product' s serial number]

LOT: [insert product' s lot number]

EXP: [insert product' s expiration date]

- b. The linear barcode is missing on the carton labeling. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to each individual carton labeling in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

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/s/

MADHURI R PATEL
11/06/2023 02:26:55 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 2/23/23

To: H. F. Van Horn III, Pharm D, MBA, Regulatory Health Project Manager
Division of Regulatory Operations (DRO) for Division of Dermatology and
Dentistry (DDD)

Tong Li-Masters, MD, Clinical Reviewer, DDD

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRANDNAME (letibotulinumtoxinA-xxxx)
for injection, for intramuscular use

BLA: 761225

Background:

In response to DDD's consult request dated November 15, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA submission for BRANDNAME (letibotulinumtoxinA-xxxx) for injection, for intramuscular use.

Labeling: OPDP has reviewed the attached proposed PI emailed to OPDP on January 24, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on February 2, 2023.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on February 23, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 301-796-1233 or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 1, 2023

To: H.F. Van Horn III, PharmD, MBA
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Ruth Mayrosh, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

James Dvorsky, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TRADENAME (letibotulinumtoxinA-xxxx)

Dosage Form and Route: for injection, for intramuscular use

Application Type/Number: BLA 761225

Applicant: Hugel, Inc.

1 INTRODUCTION

On October 6, 2022, Hugel, Inc., submitted for the Agency's review a Class 2 Resubmission for their proposed Biologics License Application (BLA) 761225 for TRADENAME (letibotulinumtoxinA-xxxx) for injection. The purpose of this resubmission is to address the deficiencies identified in the Complete Response (CR) letter issued by the Agency on March 31, 2022. The proposed indication for TRADENAME (letibotulinumtoxinA-xxxx) for injection is for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on November 15, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (letibotulinumtoxinA-xxxx) for injection, for intramuscular use.

2 MATERIAL REVIEWED

- Draft TRADENAME (letibotulinumtoxinA-xxxx) for injection MG received on October 6, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 24, 2023.
- Draft TRADENAME (letibotulinumtoxinA-xxxx) for injection Prescribing Information (PI) received on October 6, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 24, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
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JAMES S DVORSKY
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RUTH I MAYROSH
02/02/2023 08:09:49 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 20, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761225
Product Name, Dosage Form, and Strength:	Letybo (letibotulinumtoxinA-xxxx) ^a for injection, 50 units/vial and 100 units/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hugel, Inc.
FDA Received Date:	March 31, 2021, July 30, 2021, and October 6, 2022
TTT ID #:	2022-2294
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD, RPh
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

^a The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder letibotulinumtoxinA-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product

1 REASON FOR REVIEW

As part of the approval process for Letybo (letibotulinumtoxinA-xxxx) for injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Letybo prescribing information (PI), medication guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND/REGULATORY HISTORY

BLA 761225 is a 351(a) BLA submitted under section 351(a) of the Public Health Service Act on March 31, 2021. DMEPA's conducted a previous review on September 3, 2021; however, the recommendations were not conveyed to the Applicant.^b A Complete Response (CR) letter was issued by the Agency on March 31, 2022, because of facility inspection, microbiology, and product quality issues. The Applicant submitted a Class 2 resubmission on October 6, 2022, in response to the March 31, 2022.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling. We note only container labels were submitted during the current review cycle

^b Patel, M. Label and Labeling Review for Letybo (BLA 761225). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 03. OSE RCM No.: 2021-986.

and we maintain our previous recommendations for the previously and currently submitted labels and labeling. We note that the labels and labeling can be improved to facilitate product identification, to prevent deteriorated drug errors, and to increase the prominence of important information (e.g. nonproprietary name). The Applicant is proposing to market 50 units/vial and 100 units/ vial strength presentations. We note that the proposed dosing is 20 Units per treatment session (4 units into each of the 5 sites). The product strength 50 units/vial and 100 units/vial is incongruent with the dosage and administration of the product as such the proposed strengths may be prone to medication dosing and administration errors. During the previous review cycle, we communicated this concern to clinical review team during the internal midcycle meeting. The clinical team stated this was allowed for other botulinumtoxin products. We conclude that the risk for potential dosing errors is minimal as this is administered by health care providers and the product will be labeled for single dose, discard unused portion.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved, and we provided recommendations below in Section 4.1 for the the Applicant to address our concerns.

4.1 RECOMMENDATIONS FOR HUGEL, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. As presented the product strength lack prominence and the large circle graphics



on the carton labeling compete in prominence with important information (e.g. nonproprietary name, strength, etc). Additionally, the 50 units/vial and 100 units/vial strengths are not well differentiated. Hence,

- a. Revise the product strength presentation per 21 CFR 201.15(a)(6).
- b. Ensure, there is adequate differentiation between the 50 units/vial and 100 units/vial strengths. Consider the use of different colors, boxing, or some other means to provide adequate differentiation.

B. Container Labels

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to

be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

C. Carton Labeling

1. Revise and bold the reconstituted storage statement “Unused reconstituted Letybo vials must be refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light (b) (4) Do not freeze reconstituted Letybo. Discard 24 hours after reconstitution.”. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked. Additionally, we note the storage information for the unopened vial and the storage information for the reconstituted product are on two different panels. To minimize medication errors related to incorrect storage, we recommend combined and placing both storage instructions on one panel.
2. We note the carton contains incomplete instructions for reconstituting the product. The amount of diluent and the resultant concentration (XX mg/mL) should be included on the carton, if space permits. Consider adding these instructions on the side panel of the carton labeling to inform persons responsible for preparing the product what volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted.
3. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The human-readable product identifier contains the NDC, serial number, lot, and expiration date. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode.
NDC: [insert product’ s NDC]
SERIAL: [insert product’ s serial number]
LOT: [insert product’ s lot number]
EXP: [insert product’ s expiration date]

¹ The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Letybo received on July 30, 2022, from Hugel, Inc..

Table 1. Relevant Product Information for Letybo	
Initial Approval Date	N/A
Active Ingredient	letibotulinumtoxinA-wlbq
Indication	temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.
Route of Administration	intramuscularly
Dosage Form	for injection
Strength	50 units/vial and 100 units/vial
Dose and Frequency	0.1 mL (4 Units) intramuscularly into each of 5 sites, the inferomedial and superior middle of each corrugator and one in the mid-line of the procerus muscle for a total dose of 20 Units
How Supplied	freeze-dried powder supplied in a single-dose vial in the following sizes: 50 Units (NDC 81165-050-01) 100 Units (NDC 81165-100-01)
Storage	Unopened vials should be stored in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.
Container Closure	single-dose vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 5, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “761225”. Our search identified 1 previous review^c, and we considered our previous recommendations to see if they are applicable for this current review.

Table 5. Summary of Previous DMEPA Reviews for Letybo		
Record #	Review Date	Summary of Recommendations
OSE RCM# 2021-986	2021 SEP 03	We conclude that the proposed label and labeling can be improved, and we provided recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

^c Patel, M. Label and Labeling Review for Letybo (BLA 761225). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 03. OSE RCM No.: 2021-986.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Letybo labels and labeling submitted by Hugel, Inc..

- Container label received on October 6, 2022
- Carton labeling received on March 31, 2021
- Medication Guide and Prescribing Information (Image not shown) received on July 30, 2021, available from <\\CDSESUB1\EVSPROD\bla761225\0006\m1\us\114-labeling\draft\labeling\letibotulinumtoxina-bla-pi-13jul2021-tracked-changes.pdf>

F.2 Label and Labeling Images

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^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CORWIN D HOWARD
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MADHURI R PATEL
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: April 1, 2022

To: Tong Li-Masters, MD/Clinical Reviewer, M.D.
Division of Dermatology and Dentistry (DDD)

H.F. Van Horn, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for letibotulinumtoxin A

BLA: 761225

This memo is in response to Division of Dermatology and Dentistry (DDD) labeling consult request for letibotulinumtoxin A dated May 13, 2021. Reference is made to a Complete Response letter that was issued on March 31, 2022. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DDD submit a new consult request during the subsequent review cycle. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
04/01/2022 11:14:23 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: March 9, 2022

To: H. F. Van Horn III, Pharm D, MBA
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): TRADENAME (letibotulinumtoxinA)

Dosage Form and Route: for injection, for intramuscular use

Application Type/Number: BLA 761225

Applicant: Hugel, Inc. c/o Strategic Drug Development Service, LLC

1 INTRODUCTION

On March 31, 2021, Hugel, Inc. c/o Strategic Drug Development Service, LLC submitted for the Agency's review an original Biologics License Application (BLA) for TRADENAME (letibotulinumtoxinA) for injection indicated for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

On May 13, 2021, the Division of Dermatology and Dentistry (DDD) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TRADENAME (letibotulinumtoxinA) for injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for TRADENAME (letibotulinumtoxinA) for injection.

2 CONCLUSIONS

Due to outstanding deficiencies, Division of Dermatology and Dentistry (DDD) plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SUSAN W REDWOOD
03/09/2022 01:03:18 PM

BARBARA A FULLER
03/09/2022 01:17:06 PM

Clinical Inspection Summary

Date	2/18/2022
From	Phil Phuc Nguyen, M.D., Medical Officer Karen Bleich, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Acting Branch Chief/ Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Tong Li-Masters M.D., Medical Officer Snezana Trajkovic M.D., Team Lead Kendall Marcus, M.D., Division Director Division of Dermatology and Dentistry
BLA	761225
Applicant	Hugel Inc.
Drug	BoNT/A-DP; letibotulinumtoxin A
NME	Yes
Therapeutic Classification	Neuromuscular blocker
Proposed Indication	Temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults
Consultation Request Date	5/27/2021
Summary Goal Date	2/28/2022
Action Goal Date	2/28/2022
PDUFA Date	3/31/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Hugel Inc has submitted data from three phase-3 studies to the Agency in support of a biologics license application (BLA 761225) for letibotulinumtoxin A injection, for the indication of temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults. Three clinical investigators (Drs. Kaufman-Janette, Schlessinger, and Cox) were selected from two of the phase-3 studies for surveillance clinical inspections.

Based on these inspections, studies BLESS I and BLESS III IA appear to have been adequately conducted and the study data generated by the inspected entities appear acceptable in support of the respective indication in the BLA.

II. BACKGROUND

BoNT/A-DP (Letibotulinumtoxin A) is a serotype-A botulinum toxin derived from Clostridium botulinum strain CBFC26. Per the sponsor, it is defined as a new biological product and not a biosimilar of existing botulinum toxin products. Botulinum toxins generally have been shown to weaken overactive underlying muscle contraction, and thus are used to temporarily reduce the appearance of glabellar wrinkle lines between the eyebrows which often become more prominent with age.

Data from three identical, randomized, double-blinded, placebo-controlled multinational studies (Studies BLESS I, II, and BLESS III IA) were submitted in support of this application. Clinical Investigators were selected from Study BLESS I and BLESS III IA for surveillance inspections.

Per the protocols, the primary efficacy endpoint is the proportion of subjects (responders) with a Fitzpatrick wrinkle scale (FWS) score of 0 or 1 and an improvement ≥ 2 points in the maximum frown FWS score at Week 4 visit relative to baseline, based on both the investigator's and the subject's in-clinic assessments.

Eligible subjects were to be non-pregnant adults age 18 to 75 at the time of screening, with moderate to severe glabellar frown lines at maximum frown FWS score of 2 or 3. Subjects were to be excluded if they had previous botulinum toxin treatment within 12 months prior to screening and/or systemic conditions which may be worsened with exposure to botulinum toxin.

Subjects were to be randomized in a 3:1 ratio to receive BoNT/A-DP treatment vs placebo, with a maximum of 4 treatments over the duration of study. During the double-blind period called Cycle 1, subjects were to receive a single treatment, and up to 3 subsequent treatments in the following cycles of the open-label extension study. The duration of study participation for each subject was up to 14 calendar days of screening period, followed by 48 to 60 weeks of treatment. Each cycle was to last at least 12 weeks and could be prolonged in 4-week increments, depending on treatment effect. Re-treatment was to be possible until study-week 48.

Assessments were to be performed at the Screening Visit and then on the day of randomization, at Weeks 1, 2, 4, and 8, and on the day of re-evaluation ≥ 12 weeks after the first treatment. Photographs of subjects' glabellar lines were to be taken during the double-blind Cycle 1 to allow for specialist review by an Independent Review Panel, before treatment at randomization (day of first treatment), at Weeks 2 and 4, and on the day of evaluation for retreatment (≥ 12 weeks after the first/previous treatment).

Study CPH-301-201030 (BLESS I)

- Study Title: *Randomized Double-blind Phase 3 Study to Assess the Efficacy and Safety of BoNT/A-DP in the Treatment of Glabellar Lines in Comparison With Placebo, Followed by an Open Label Extension Study*

Per the study report, a total of 708 subjects were randomized and 704 received treatments. The study was conducted at 18 study centers in the US and abroad. The first subject was randomized March 21, 2016, and the last subject completed November 16, 2017.

Study CPH-303-201400 (BLESS III IA)

- Study Title: *Randomized Double-blind Phase 3 Study to Assess the Efficacy and Safety of BoNT/A-DP in the Treatment of Glabellar Lines in Comparison with Placebo, Followed by an Open-label Extension Study*

Per the study report, a total of 355 subjects were randomized and received treatments. The study was conducted across 7 study centers in the US and Austria. The first subject was randomized May 06, 2019, and data cut-off for Interim Analysis was February 10, 2020.

III. RESULTS (by Site)

1. Joely Kaufman-Janette M.D.

Skin Research Institute LLC, 4425 Ponce De Leon Boulevard, Suite 200,
Coral Gables, FL 33146

Study: CPH-303-201400 (BLESS III IA)

Site Number: B3113

Dates of Inspection: 10/18/2021 to 10/21/2021

This inspection was conducted on-site. At the time of the inspection, 61 subjects were screened, 47 enrolled and 43 subjects finished the study. Efficacy data for 22 of enrolled subjects were reviewed against source data, with no discrepancies. There was no evidence of under-reporting of protocol deviations. The inspection revealed no deficiencies with maintenance of the blind.

Two adverse events were identified by the CI but were not included in the individual patient-level data line listings submitted to the Agency. According to the AE reporting forms, both AEs were reported to the CRO prior to the data lock date (2/10/2020).

Subject / Arm	Adverse Event / Severity	Dates	Notes
(b) (6) / placebo	Right Eyebrow Ptosis/mild	(b) (6)	Adverse Event of Significant Interest (AESI), Cycle 2, spontaneously resolved
(b) (6) / treatment	Elevated GGT/mild		Cycle 2, spontaneously resolved

Reviewer comments: The events were mild in severity and spontaneously resolved. While the elevated GGT was not reported as AE, it is appropriately captured in the lab data and was determined by the CI to not be related to the study treatment.

Except the findings described above, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

2. Joel Schlessinger M.D.
2802 Oak View Drive Omaha, NE 68144
Study: CPH-301-201030 (BLESS I)
Site Number: B1110
Dates of Inspection: 10/04/2021 to 10/08/2021

This inspection was conducted on-site. At the time of the inspection, 52 subjects were screened and 44 enrolled into the study. There were no issues with the informed consent process. Data listings for 15 subjects were compared against source data, with no discrepancies. There was no evidence of under-reporting of adverse events or under-reported protocol deviations. The inspection revealed no deficiencies with maintenance of the blind.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

3. Sue Ellen Cox M.D.
Aesthetic Solutions P.A. Ste 101, 5821 Farrington Road, Chapel Hill, NC 27517
Study: CPH-303-201400 (BLESS III IA)
Site Number: B3111
Dates of Inspection: 10/04/2021 to 10/07/2021

This inspection was conducted on-site. At the time of the inspection, 50 subjects were screened and 44 enrolled into the study. Data listings for 14 subjects were compared against source data, with no discrepancies. There was no evidence of under-reporting of adverse events or under-reported protocol deviations. The inspection revealed no deficiencies with maintenance of the blind. There were no major issues with the informed consent process. There was one minor issue regarding the IP drug accountability record that does not impact subject safety or data integrity.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

{See appended electronic signature page}
Phuc Nguyen, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*
Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE: *{See appended electronic signature page}*
Kassa Ayalew, M.D., M.P.H
Division Director / Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
DDD / Division Director / Kendall Marcus
DDD / Team Lead / Snezana Trajkovic
DDD / Clinical Reviewer / Tong Li-Masters
DRO / Regulatory Project Manager / Howard Van Horn III

OSI / DCCE / Division Director / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Karen Bleich
OSI / DCCE / GCPAB Reviewer / Phillip Phuc Nguyen
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / DCCE / Database Project Manager / Dana Walters

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/s/

PHUC L NGUYEN
02/25/2022 12:26:51 PM

KAREN B BLEICH
02/25/2022 02:02:07 PM

KASSA AYALEW
02/25/2022 04:13:11 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
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and Reproductive Medicine
Office of New Drugs
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Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatrics and Maternal Health Review

Date: 9/24/2021 **Date consulted:** 8/17/2021

From: Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health (DPMH)

To: Division of Dermatology and Dentistry (DDD)

Drug: letibotulinumtoxinA for injection

BLA: 761225

Applicant: Hugel, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: For the temporary improvement of the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activities in adults.

Materials

Reviewed:

- Applicant submission package and draft labeling submitted on March 31, 2021
- DPMH Consult request dated August 17, 2021, DARRTS Reference ID 4842728
- DPMH Consult Review of DWP-450 (a Botulinum Toxin Type A (BTAA) product), BLA 761085, Jane Liedtka MD, December 18, 2017. DARRTS Reference ID 4197258

Consult Question: “Review of labeling.”

INTRODUCTION AND BACKGROUND

On March 31, 2021, Hugel, Inc., submitted an original BLA for letibotulinumtoxinA, BLA 761225. DDD consulted DPMH on August 17, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

LetibotulinumtoxinA BLA 761225 is submitted as an original BLA for the proposed indication of temporary improvement of the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activities in adults.

LetibotulinumtoxinA A Drug Characteristics¹

Drug Class	LetibotulinumtoxinA is an acetylcholine release inhibitor and neuromuscular blocking agent.
Dosage and Administration	Administer 0.1mL locally into corrugator and procerus muscles by intramuscular injection into each of five sites, for a total dose of 20 units.
Mechanism of action	LetibotulinumtoxinA blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, letibotulinumtoxinA produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity.
Molecular weight	~ 900 kDaltons
Protein Binding	Not reported
Half-life	Not reported

REVIEW

PREGNANCY

Nonclinical Experience

In an animal reproduction study, intramuscular administration of letibotulinumtoxinA to rats during pregnancy resulted in adverse effects on fetal growth (decreased fetal body weight and skeletal ossification) at maternally toxic doses 3 times the maximum recommended human dose (MRHD).

The reader is referred to the Pharmacology/Toxicology review by Xinguang (Cindy) Li PhD, and Barbara Hill PhD.

¹ Information reviewed with Clinical Pharmacology and Pharmacotoxicology Teams

Data from Clinical Trials

There were four pregnancies reported, two exposed to letibotulinumtoxinA, during the clinical trials. All pregnancies were first trimester exposures (drug was discontinued upon discovery of pregnancy) and resulted in live births. There were no reports of major malformations.

Review of Literature

Applicant's Review of the Literature

The Applicant performed a search of the published literature using the PubMed database from January 1, 2017 to September 9, 2021, using the search terms, "letibotulinumtoxinA," or "botulinum" and "pregnancy."

The cases found in the literature search are discussed under DPMH Review of the Literature section of this document. There were no cases related to letibotulinumtoxinA exposure and pregnancy. A table with the Applicant's literature results is located in Appendix A.

DPMH's Review of the Literature

DPMH performed a search of the literature using PubMed and Embase using the search terms "letibotulinumtoxinA," "botulinum A toxin," and "pregnancy," "stillbirth," "miscarriage," "congenital malformations," and "pregnancy outcomes." DPMH had previously performed a search of the literature on botulinum toxin A and pregnancy through December 2017 (see DPMH Consult Review of DWP-450 [a Botulinum Toxin Type A (BTAA) product], Jane Liedtka MD, December 18, 2017. DARRTS Reference ID 4197258). An updated search for cases of pregnancies exposed to botulinum A toxin since December 2017 was also performed.

The search did not find in any cases of pregnancy related to exposure to letibotulinumtoxinA. The search located the studies described in the Reviewer's table below.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
Wong HT, et al. ² 2020 UK	Prospective case series from a study of 972 patient receiving treatment for migraine over a 9 year timeframe (average prospective	45 patients exposed to onabotulinumtoxinA ³ within 3 months of conception	45 patients all with first trimester exposure; 32 of which continued treatment with onabotulinumtoxinA throughout pregnancy	1 patient had a miscarriage at 9 weeks' gestation; same patient continued treatment through a second pregnancy with delivery of healthy infant. Remaining patients had live births – no congenital malformations	Small sample size, no control group

² Wong HT, et al. OnabotulinumtoxinA for chronic migraine during pregnancy: a real world experience on 45 patients. J Headache and Pain. 2020;21:129

³ OnabotulinumtoxinA is made from a different strain of *Clostridium botulinum* but has a similar mechanism of action to letibotulinumtoxinA

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
	follow-up 3.5 years)				
Cardon BR, et al. ⁴ 2021 USA	Case series	3 cases of pregnancies exposed to botulinum A toxin. <u>Case #1</u> : 37 year-old woman with spasmodic dysphonia <u>Case #2</u> : 32 year-old woman with spasmodic dysphonia <u>Case #3</u> : 33 year-old woman with spasmodic dysphonia	<u>Case #1</u> - injections at 4 weeks' and 34 weeks' gestation <u>Case #2</u> - injections at 9 weeks' and 34 weeks' gestation and 7 weeks' postpartum. Case #3: injections on the day of conception, 14 weeks' gestation, and 3 weeks' postpartum.	<u>Case #1</u> : diagnosed with intra uterine growth restriction, vaginal delivery at 37 weeks', healthy infant <u>Case #2</u> : spontaneous vaginal delivery at 38 weeks' gestation. Infant Apgar scores were 8 and 9, at 1 and 5 minutes, respectively. Normal milestones through age 3. <u>Case #3</u> : Preterm labor at 35 weeks' after tocolysis delivered at 36 weeks' gestation, a healthy infant with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Follow-up at 5 years revealed a congenital kidney abnormality. Normal milestones through age 5.	Small case series, no controls.
Brin MF, et al. ⁵ 2021 USA	Pharmacovigilance database (Allergan global safety database)	913 pregnancies reported from 1/1/1990 through 12/31/2018)	Most common indications were cosmetic (35.3%), migraine (30.3%), and movement disorders (12.1%)	Of the 195 prospective cases with 197 fetuses there were: - 152 live births - 32 spontaneous abortions - 13 elective abortions Among the live births there was one major birth defect, two minor defects and one birth complication. (None of these were described.)	This was a post-additional details were not provided.

Reviewer's Table

⁴ Cardon BR, et al. Case series of botulinum toxin A administered to pregnant patients and review of the literature. Facial Plastic Surgery and Aesthetic Medicine. 2021;23(3):187-190.

⁵ Brin MF, et al. Pregnancy outcomes following exposure to onabotulinumtoxinA update: 29 years of safety observation. Toxicon. 2020;190 Suppl 1 (S10-S11).

Reviewer comment:

Previous DPMH literature reviews of botulinum toxin A have not reported an increased risk for adverse maternal or fetal outcomes with botulinum toxin A use pregnancy. Botulinum toxin products are used for local injection; systemic absorption is likely to be low since patients do not experience botulism when doses are administered consistent with approved labeling. An updated search of the literature is consistent with previous reports. There are no published reports on letibotulinumtoxinA and pregnancy. The four pregnancies exposed during the clinical trials resulted in live births; there were no reports of congenital malformations.

LACTATION

Nonclinical Experience

Animal lactation studies with letibotulinumtoxinA have not been performed.

Data from Clinical Trials

There were no cases of lactation reported from the clinical trials.

Review of Literature

Applicant's Review of the Literature

The Applicant performed a search of the published literature using the PubMed database from January 1, 2017 to September 9, 2021, using the search terms, “letibotulinumtoxinA,” or “botulinum” and “breast feed,” or “lactation.”

The Applicant referenced the article in LactMed on botulinum toxin and breastfeeding. The LactMed article is discussed under DPMH's Review of the Literature below.

DPMH's Review of the Literature

DPMH performed a search of the literature using PubMed and Embase using the search terms “letibotulinumtoxinA,” and “lactation,” or “breastfeeding.” DPMH had previously performed a search of the literature on botulinum toxin A and lactation through December 2017 (see DPMH Consult Review of DWP-450 [a Botulinum Toxin Type A (BTTA) product], Jane Liedtka MD, December 18, 2017. DARRTS Reference ID 4197258). An updated search for cases of lactation and botulinum A toxin since December 2017 was also performed.

Hale's⁶ rates botulinum toxin A as, “L3-No Data- Probably Compatible.”

Briggs⁷ states, “No human data, probably compatible.”

LactMed⁸ states in its Summary of Use:

“No data exist on the medical use of botulin A (botulinum toxin) during breastfeeding. However, it is not detected systemically after intramuscular injection thus excretion into breast milk is considered unlikely. Breastfeeding appears to protect infants against

⁶ Hale's Medications and Mother's Milk <https://www.halesmeds.com/monographs/60934?q=botuli> accessed 9/12/2021.

⁷ Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 2011, .

⁸ <https://www.ncbi.nlm.nih.gov/books/NBK501400/#:~:text=Summary%20of%20Use%20during%20Lactation.to%20protect%20infants%20against%20botulism>. Accessed 9/12/2021

botulism. One infant was safely breastfed during maternal botulism and no botulinum toxin was detectable in the mother's milk or the infant. Since doses used medically are far lower than those that cause botulism, amounts ingested by the infant, if any, are expected to be small and not cause any adverse effects in breastfed infants. No special precautions are required."

The search of the published literature did not locate any new references on botulinum A toxin and lactation or any references on letibotulinumtoxinA and lactation.

Reviewer comment:

No data are available on letibotulinumtoxinA and lactation. Data on botulinum toxin A are limited, but one case report of a lactating women with botulism indicates that it is not present in breast milk and there were no adverse effects on the infant. Given the high molecular weight of botulinum toxin and the lack of evidence of systemic absorption when approved doses are used, the risk to the infant appears to be low. DPMH recommends that the risk/benefit statement for lactation be included in labeling.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Fertility studies with animals were not conducted.

Data from Clinical Trials

No cases of infertility were reported.

Review of Literature

Applicant's Review of the Literature

The Applicant performed a search of the published literature using the PubMed database from January 1, 2017 to September 9, 2021, using the search terms, "letibotulinumtoxinA," or "botulinum" and "fertility."

The Applicant's search did not locate cases related to exposure to letibotulinumtoxinA or botulinum toxin and fertility.

DPMH's Review of the Literature

DPMH performed a search of the literature using PubMed and Embase using the search terms "letibotulinumtoxinA," and "fertility," "infertility" or "hormonal contraception." DPMH had previously performed a search of the literature on botulinum toxin A and fertility through December 2017 (see DPMH Consult Review of DWP-450 [a Botulinum Toxin Type A (BTAA) product], Jane Liedtka MD, December 18, 2017. DARRTS Reference ID 4197258). An updated search for cases of infertility and interference with hormonal contraception and botulinum A toxin since December 2017 was also performed.

No cases related to letibotulinumtoxinA and infertility or effects on hormonal contraception were located in the search. No new papers on the effects of botulinum A toxin were found.

Reviewer comment:

Previous DPMH reviews of botulinum toxin A products have not found evidence of adverse effects on fertility or hormonal contraceptive efficacy. Animal studies have not been conducted and the current literature search does not find evidence of adverse effects on fertility. Since data do not indicate that letibotulinumtoxinA or botulinum toxin A have major teratogenic effects that would necessitate pregnancy testing or contraceptive requirements, subsection 8.3 should not be included in labeling.

DISCUSSION AND CONCLUSIONS

Pregnancy

LetibotulinumtoxinA is for local injection; systemic absorption was not assessed but is expected to be low. Nonclinical data indicate an adverse effect on rat fetuses that are interpreted as secondary to maternal toxicity. Human data are limited to four cases of pregnancy exposure that occurred during the clinical trials. All resulted in live births without major congenital malformations. There are no published cases of pregnancy exposure to letibotulinumtoxinA. Limited published data do not indicate that botulinum toxin is a major teratogen or produces adverse maternal or fetal outcomes. LetibotulinumtoxinA is a large molecule, with a molecular weight of approximately 900 kilo Daltons, and would not be expected to cross the placenta.

Botulinum toxin products have been marketed in the U.S. since the early 1990's⁹ without an established association with major birth defects, fetal loss, or other adverse maternal or fetal effects. Therefore, DPMH is not recommending postmarketing pregnancy studies.

Lactation

No lactation studies with letibotulinumtoxinA have been conducted in animals. A single case report described a lactating woman with foodborne botulism who had no measurable amount of botulinum toxin in breast milk and no adverse effects on the infant. LetibotulinumtoxinA has a high molecular weight, and there is lack of systemic absorption when used at approved doses. DPMH recommends the following statement be included in labeling,

“The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for [BRAND NAME] and any potential effects on the breastfed infant from [BRAND NAME] or from the underlying maternal condition.”

Given the expected lack of systemic absorption when used at approved doses, a lactation study is not recommended.

Females and Males of Reproductive Potential

Animal studies have not been conducted to evaluate the effect of letibotulinumtoxinA on fertility. There are no published cases in the literature indicating an adverse effects of botulinum toxin on fertility or on the effectiveness of hormonal contraception. DPMH recommends that subsection 8.3 be omitted from labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2, of labeling for compliance with the PLLR (see below). DPMH refers to the final BLA action for final labeling.

⁹ Botox (onabotulinumtoxinA) BLA 103000 approval 12/09/1991

APPENDIX A- Applicant's Search of the Published Literature

Author, Year	Type of Study (design)	Number of Subjects Exposed	Endpoints and Outcomes of Study (Including Point Estimates, P-values, and Confidence Intervals, if Available)
Botulinum poisoning (Drugs and Lactation Database [LactMed]), 2021	Review article	Not applicable	No risk for breast-fed infants was identified when mother had botulism.
Koo, 2021	Mouse study	Not applicable	Endothelial cell tube formation and sprouting in the presence of botulinum toxin. Intrauterine BoTA administration significantly induced endometrial angiogenesis displaying increased numbers of vessel formation and expression levels of related marker genes. Moreover, BoTA intrauterine application promoted the endometrial receptivity, and the rates of embryo implantation were improved with BoTA treatment with no morphologically retarded embryos. Intrauterine BoTA treatment has a beneficial effect on vascular reconstruction of functional endometrium prior to embryo implantation by increasing endometrial blood flow near the uterine cavity
Cardon, 2021	Case reports and review of literature	3 case reports of medically necessary botulinum toxin during pregnancy	Evaluation of health status of children after intrauterine exposure. No evidence of harm to the mothers or fetuses were found in our series, including data from pregnancy and birth records using standard measures of gestation, APGAR scores, neonatal intensive care unit stay, and time until discharge. Clinical data for 3-5 years were available for the children. No evidence of muscular weakness was noted and all diagnoses were listed.
Wong, 2020	Case reports	45 subjects treated with onabotulinumtoxinA for chronic migraine at a single center	Mode of delivery, birth weight, congenital malformation, and any other unexpected outcomes, Apart from 1 miscarriage in the treatment group, all patients had full term healthy babies of normal birth weight and no congenital malformations.
Botulin A (Drugs and Lactation Database [LactMed]), 2020	Review article	Not applicable	Maternal Levels. Published information on the medical use of botulin A during breastfeeding was not found as of the revision date. Type A botulinum toxin was detected in the blood and stools of a nursing mother after ingesting fermented salmon eggs. She was given 2 vials of trivalent botulism antitoxin, 1 intravenously and 1 intramuscularly. A milk

Author, Year	Type of Study (design)	Number of Subjects Exposed	Endpoints and Outcomes of Study (Including Point Estimates, P-values, and Confidence Intervals, if Available)
			sample obtained 3 days after the onset of her illness and 4 hours after administration of botulinum antitoxin had no detectable botulinum toxin nor botulism organisms. Infant Levels. Type A botulinum toxin was detected in the blood and stools of a nursing mother after ingesting fermented salmon eggs. No botulinum toxin was detected in the breastfed infant's blood or stool on the day the mother was admitted to the hospital (3 days after the onset of illness) and no botulism organisms were detected in the infant's stools.
RimabotulinumtoxinB (Drugs and Lactation Database [LactMed]), 2020	Review article	Not applicable	No information specific to rimabotulinumtoxinB.
PrabotulinumtoxinA (Drugs and Lactation Database [LactMed]), 2020	Review article	Not applicable	No information specific to prabotulinumtoxinA
OnabotulinumtoxinA (Drugs and Lactation Database [LactMed]), 2020	Review article	Not applicable	No information specific to onabotulinumtoxinA.
IncobotulinumtoxinA (Drugs and Lactation Database [LactMed]), 2020	Review article	Not applicable	No information specific to IncobotulinumtoxinA.
AbotulinumtoxinA (Drugs and Lactation Database [LactMed]), 2020	Review article	Not applicable	No information specific to abotulinumtoxinA
Li, 2020	Literature review	Not provided	Maternal or fetal complications in pregnant patients treated with BoNT.

Author, Year	Type of Study (design)	Number of Subjects Exposed	Endpoints and Outcomes of Study (Including Point Estimates, P-values, and Confidence Intervals, if Available)
			BoNT injection does not increase the risk of complications in pregnant women and fetuses.
PrabotulinumtoxinA (Jeuveau) for frown lines, 2019	Review article	Not applicable	Not applicable No adverse fetal effects were observed when pregnant rats were injected with prabotulinumtoxinA at doses 12 times the maximum recommended human dose. Case reports of botulinum toxin use during pregnancy have generally found no adverse effects on the fetus or newborn.
Neubert, 2019	Case report	1 case report of botulinum toxin use for type II achalasia and solid/liquid dysphagia during pregnancy	Maternal and fetal outcome The patient experienced no complications and fetal heart tones remained normal.
Kroumpouzos, 2018	Literature review	Not provided	Maternal and fetal outcome. Botulism has been reported in 15 pregnant patients and was not associated with birth defects, neonatal loss, or congenital botulism (Badellet al., 2017). In two cases of maternal botulism, infant serum was taken, and no botulinum toxin was detected (Tan et al., 2013). A large Allergan series of BTX-A during pregnancy (232 exposed patients during pregnancy) was published recently and showed rates of spontaneous abortion and fetal defects similar to background rates in the general population (Brin et al., 2016). These data indicate that BTX-A administration during pregnancy is likely not associated with fetal/ neonatal loss and birth defects.
Jain, 2017	Case reports and review of literature	2 case reports of botulinum toxin A treatment during pregnancy for post-herpetic neuralgia	Both the babies delivered were normal and are growing up normally.

Author, Year	Type of Study (design)	Number of Subjects Exposed	Endpoints and Outcomes of Study (Including Point Estimates, P-values, and Confidence Intervals, if Available)
Watson, 2017	Literature review on potential biological threat of botulism	Not provided	Effects of botulism in pregnancy. No specific findings noted.
Contarino 2017	Literature review on botulinum toxin treatment of cervical dystonia	Not provided	Maternal and fetal outcome. Results of a survey on 396 doctors showed that a total of 16 pregnant women had been treated with BoNT, primarily in the first trimester. One patient (8.3%) had a miscarriage, while the other patients gave birth to healthy children after full-term pregnancies. The overall risk of miscarriage, regardless of the cause, is 15–20%. In the literature, up to 25 women are described who have been treated during each stage of pregnancy: two miscarriages were reported in women with previous history of miscarriage; the other cases reported uneventful pregnancy and healthy children.
Trivedi, 2017	Literature review on the safety of cosmetic procedures during pregnancy and lactation	Not provided	Maternal and fetal outcome Multiple case reports suggest no harm to fetus in either cosmetic botulinum toxin or other medical indications (migraine prophylaxis, achalasia, cervical dystonia) in majority of patients. Miscarriages reported in two patients in two individual reports, but relation to toxin injection unclear. High doses of onabotulinum toxin (N600 U) associated with systemic weakness.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 3, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761225
Product Name, Dosage Form, and Strength:	Letybo (letibotulinumtoxinA-xxxx) ^a for injection, 50 units/vial and 100 units/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hugel, Inc.
FDA Received Date:	March 31, 2021 and July 30, 2021
OSE RCM #:	2021-986
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

^a The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder "letibotulinumtoxinA-xxxx" is used throughout this review to refer to the non-proprietary name for this product and not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

As part of the approval process for Letybo (letibotulinumtoxinA-xxxx) for injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Letybo prescribing information (PI), medication guide (MG), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling. We note that the labels and labeling can be improved to facilitate product identification, to prevent deteriorated drug errors, and to increase the prominence of important information (e.g. nonproprietary name). The Applicant is proposing to market 50 units/vial and 100 units/ vial strength presentations. We note that the proposed dosing is 20 Units per treatment session (4 units into each of the 5 sites). The product strength 50 units/vial and 100 units/vial is incongruent with the dosage and administration of the product as such the proposed strengths may be prone to medication dosing and administration errors. We communicated this concern to clinical review team during the internal midcycle meeting. The clinical team stated this was allowed for other botulinumtoxin products. We conclude that the risk for potential dosing errors is minimal as this is administered by health care providers and the product will be labeled for single dose, discard unused portion.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved and we provided recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. General Comments

1. The Applicant is proposing to market 50 units/vial and 100 units/ vial strength presentations. We note that the proposed dosing is 20 Units per treatment session (4 units into each of the 5 sites). The product strength 50 units/vial and 100 units/vial is incongruent with the dosage and administration of the product as such the proposed strengths may be prone to medication dosing and administration errors. We communicated this concern to clinical review team during the internal midcycle meeting. We defer to DDD to determine the need for a 50 units per vial and 100 units per vial strength presentations.

4.2 RECOMMENDATIONS FOR HUGEL, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. As presented the product strength lack prominence and the large circle graphics  on the carton labeling compete in prominence with important information (e.g. nonproprietary name, strength, etc). Additionally, the 50 units/vial and 100 units/vial strengths are not well differentiated. Hence,
 - a. Revise the product strength presentation per 21 CFR 201.15(a)(6).
 - b. Ensure, there is adequate differentiation between the 50 units/vial and 100 units/vial strengths. Consider the use of different colors, boxing, or some other means to provide adequate differentiation.

B. Container Labels

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM

if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

C. Carton Labeling

1. Revise and bold the reconstituted storage statement “Unused reconstituted Letybo vials must be refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light (b) (4) Do not freeze reconstituted Letybo. Discard 24 hours after reconstitution.”. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked. Additionally, we note the storage information for the unopened vial and the storage information for the reconstituted product are on two different panels. To minimize medication errors related to incorrect storage, we recommend combined and placing both storage instructions on one panel.
2. We note the carton contains incomplete instructions for reconstituting the product. The amount of diluent and the resultant concentration (XX mg/mL) should be included on the carton, if space permits. Consider adding these instructions on the side panel of the carton labeling to inform persons responsible for preparing the product what volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted.
3. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The human-readable product identifier contains the NDC, serial number, lot, and expiration date. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode.
NDC: [insert product’ s NDC]
SERIAL: [insert product’ s serial number]
LOT: [insert product’ s lot number]
EXP: [insert product’ s expiration date]

¹ The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Letybo received on July 30, 2021 from Hugel, Inc..

Table 2. Relevant Product Information for Letybo	
Initial Approval Date	N/A
Nonproprietary Name	letibotulinumtoxinA-xxxx
Indication	temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients
Route of Administration	intramuscularly
Dosage Form	for injection
Strength	50 units/vial and 100 units/vial
Dose and Frequency	0.1 mL (4 Units) intramuscularly into each of 5 sites, the inferomedial and superior middle of each corrugator and one in the mid-line of the procerus muscle for a total dose of 20 Units
How Supplied	freeze-dried powder supplied in a single-dose vial in the following sizes: 50 Units (NDC 81165-050-01) 100 Units (NDC 81165-100-01)
Storage	Unopened vials should be stored in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.
Container Closure	n/a

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Letybo labels and labeling submitted by Hugel, Inc..

- Container labels received on March 31, 2021
- Carton labeling received on March 31, 2021
- Prescribing Information and Medication Guide (Images not shown) received on July 30, 2021, available from <\\CDSESUB1\evsprod\bla761225\0006\m1\us\114-labeling\draft\labeling\letibotulinumtoxina-bla-pi-13jul2021-tracked-changes.pdf>

G.2 Label and Labeling Images

(b) (4)



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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