

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761146Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
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:	June 24, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761146
Product Name and Strength:	Qwo (collagenase clostridium histolyticum-aes) for injection, 0.92 mg/vial and 1.84 mg/vial
Applicant/Sponsor Name:	Endo Global Aesthetics Limited
OSE RCM #:	2019-1865-2
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on June 23, 2020 for Qwo. Division of Dermatology and Dentistry (DDD) requested that we review the revised carton labeling for Qwo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are related to the format of the expiration date which has been modified since our previous label and labeling review memorandum.^a

2 CONCLUSION

In this submission, the Applicant has modified the format of the expiration date to YYYY-MM using numerical characters from a previous proposed format of YYYY-MM-DD citing in-place processes and current validation on the equipment at the manufacturing site. We find the revised labeling acceptable from a medication error perspective and have no additional recommendations at this time.

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS)
Immediately Following this Page

^a Patel M. Label and Labeling Review MEMO for Qwo (BLA 761146). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 12. RCM No.: 2019-1865-1.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
06/24/2020 09:30:38 AM

SEVAN H KOLEJIAN
06/24/2020 01:41:33 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
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:	June 12, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761146
Product Name and Strength:	Qwo (collagenase clostridium histolyticum-aaes) for injection, 0.92 mg/vial and 1.84 mg/vial
Applicant/Sponsor Name:	Endo Global Aesthetics Limited
OSE RCM #:	2019-1865-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 5, 2020 for Qwo. Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Qwo (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.^a

2 CONCLUSION

In this submission, the Applicant has also provided revised container label and carton labeling for their proposed proprietary name, Qwo. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

5 Pages of Draft Labeling have been Withheld in Full as
B4(CCI/TS) Immediately Following this Page

^a Patel M. Label and Labeling Review for collagenase clostridium histolyticum-aaes (BLA 761146). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 18. RCM No.: 2019-1865.

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/s/

MADHURI R PATEL
06/12/2020 02:41:23 PM

SEVAN H KOLEJIAN
06/12/2020 07:37:43 PM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2019411
BLA:	761146
Referenced IND for BLA:	110077
Applicant:	Endo Global Aesthetics
Established Name/Trade Name:	collagenase clostridium histolyticum (CCH)
Indication:	treatment of moderate to severe cellulite [edematous fibrosclerotic panniculopathy (EFP)] in the buttocks of adult women
Meeting Type/Deliverable:	Advice Letter/Advice to Division
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer	Melinda McCord
Clinical Team Leader (TL)	Gordana Diglisic
Review Division Project Manager:	Craig Johnson
COA Reviewer:	Mira Patel
COA TL:	Elektra Papadopoulos
COA Acting Director:	Elektra Papadopoulos
Date Consult Request Received:	11/4/2019
Date COA Briefing Package/Submission Received:	9/16/2019
Date COA Review Completed:	4/30/2020

Please check all that apply:

- ☐ Rare Disease/Orphan Designation
☐ Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to BLA 761146 for collagenase clostridium histolyticum (CCH). The proposed indication is treatment of moderate to severe cellulite [edematous fibrosclerotic panniculopathy (EFP)] in the buttocks of adult women.

The Applicant utilized the following COAs in two phase 3, randomized, multi-center, double-blind, placebo-controlled pivotal trials (Studies EN3835-302 and EN3835-303) in female adults (≥ 18 years of age) with moderate and/or severe EFP in each buttock

Table 1. COAs Included in Studies EN3835-302 and EN3835-303

COA Name (COA Type)	Concept(s)	Endpoint Position ¹	Copy of COA
Clinician-reported Photometric Cellulite Severity Scale (CR-PCSS; ClinRO)	Cellulite severity	Primary	Appendix A
Patient-reported Photometric Cellulite Severity Scale (PR-PCSS; PRO)	Cellulite severity	Primary/Secondary	Appendix B

¹ Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

COA Name (COA Type)	Concept(s)	Endpoint Position ¹	Copy of COA
Subject Self-Rating Scale (SSRS; PRO)	Cellulite appearance satisfaction	Secondary	Appendix C
Subject Global Aesthetic Improvement Scale (S-GAIS; PRO)	Global aesthetic improvement	Secondary	Appendix D
Patient-Reported Cellulite Impact Scale (PR-CIS; PRO)	Cellulite emotional/visual impact	Secondary	Appendix E

ClinRO= Clinician-reported outcome; **PRO**= Patient-reported outcome

The Applicant seeks COA labeling claims for Studies EN3835-302 and EN3835-303. The Division of Dermatology and Dentistry seeks Division of Clinical Outcome Assessment (DCOA) input on 1) the acceptability of the instruments for use as the primary efficacy endpoints (Clinician-reported Photometric Cellulite Severity Scale [CR-PCSS] and Patient-reported Photometric Cellulite Severity Scale [PR-PCSS] and the secondary efficacy endpoints (Subject Self-Rating Scale [SSRS]; (b) (4) and 2) recommendations regarding the Applicant's proposed labeling claims. Further, this review will focus only on Studies EN3835-302 and EN3835-303 since the Applicant's proposed COA-related labeling claims are related to these two studies.

This submission included the evidence dossiers describing the developmental history and measurement properties of the COAs.

The review concludes the following:

- The evidence submitted by the Applicant is sufficient to demonstrate that:
 - CR-PCSS and PR-PCSS are fit-for-purpose² to measure cellulite severity for the context of use of this drug development program. Furthermore, both instruments are adequate to support labeling claims related to the improvement of cellulite severity.
 - SSRS is fit-for-purpose² to measure cellulite emotional/visual impact for the context of use of this drug development program. Furthermore, this instrument is adequate to support labeling claims related to satisfaction of cellulite appearance.

(b) (4)

See Sections *Content Validity*, *Other Measurement Properties*, and *Interpretation of Scores* for evidence on inclusion or exclusion of instruments in product labeling.

² Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; <https://www.ncbi.nlm.nih.gov/books/NBK338448/>)

DCOA defers to Clinical and Biostatistics on whether the data in the label reflects the actual endpoints specified in the statistical analysis plans, as well as whether the quality of the COA data is up to par to support the proposed labeling claims. DCOA has provided our findings and recommendations for each of the proposed instruments in Sections *Content Validity*, *Other Measurement Properties*, and *Interpretation of Scores* below.

B. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Regulatory Background:

- At the Type C teleconference meeting held December 14, 2015, FDA identified concerns surrounding the Clinician-reported and Patient-reported Photometric Cellulite Severity scales (CR-PCSS; PR-PCSS, respectively) regarding the dissimilarities of the clinician and patient-reported assessments, as well as with the data collection methodology. The sponsor proposed to conduct additional qualitative and quantitative work on their scale to establish content validity and test-retest reliability, respectively, in which their methodological approach appeared mostly appropriate. FDA emphasized the importance of standardizing training and scale administration across clinicians and subjects.
- Based on their submission of study reports on their qualitative and quantitative work the COA review concluded that the content validity of the CR-PCSS and PR-PCSS appeared to be reasonably established.
- The Agency held an End-of-Phase 2 meeting with the sponsor on February 8, 2017 in which more data was asked of them in order to reach agreements on their endpoints for the proposed indication of treatment of EFP. A clinical information amendment was submitted on February 13, 2017 which provided information on several questions raised during the meeting. The sponsor was granted a Type C meeting to discuss this information with the Agency.
- During the meeting discussion at the guidance meeting held on June 28, 2017, the sponsor had communicated that they would conduct a live test-retest study (with an adequate number of subjects representing all levels of the scale will be recruited) to be conducted prior to phase 3. The results from this study are described within this review.
- The sponsor submitted their first special protocol assessment (SPA) request on September 29, 2017. The SPA was denied as additional results were requested, including further analyses on reliability, CR-PCSS and PR-PCSS agreement, and the generation of cumulative distribution function (CDF) plots. The key results are described within this review.
- The sponsor re-submitted the SPA on November 27, 2017. From COA perspective, the previous evidence submitted on the reliability and validity appeared sufficient to support the primary endpoint (2-point improvement in CR-PCSS and PR-PCSS). It was also concluded that the sponsor still had not provided a strong rationale that a 1-point change in the S-GAIS is a meaningful change in this instrument. The results from the CDF and PDF suggested that a 2-point change in the S-GAIS equates to a 2-point change in the PR-PCSS, which is the determinant of clinical benefit for the primary endpoint.
- The sponsor was also requested to provide development history for all tools utilized in the Phase 3 studies.

Previous COA Reviews:

- C2019443_Patel dated January 13, 2020 [DARRTS Reference ID: 4545296]
- C2018375_Daniels dated January 16, 2019 [DARRTS Reference ID: 4377228]
- C2017391_Daniels dated January 09, 2018 [DARRTS Reference ID: 4202824]
- C2017317_Daniels dated October 31, 2017 [DARRTS Reference ID: 4174884]
- C2017149_Daniels dated August 13, 2017 [DARRTS Reference ID: 4132322]
- C2017009_Daniels dated March 20, 2017 [DARRTS Reference ID: 4061497]
- AT 2015-171_Daniels dated January 13, 2016 [DARRTS Reference ID: 3866286]

Disease Background:

Edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, has been defined as a local metabolic disorder of subcutaneous tissues that results in an alteration of skin topography (Khan et al., Part I, 2010³). The condition manifests as dimpled skin particularly in the gluteal-femoral region. EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction.

Investigational Product:

CCH is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions and has the potential to be effective in lysing subdermal collagen, such as those observed in the dermal septa.

Other materials reviewed:

Current submission of COA evidence dossiers (Section 5.3.5.3) and draft product label

2 CONTEXT OF USE

2.1 Clinical Trial Population

The target population for Studies EN3835-302 and EN3835-303 are females, ≥ 18 years of age, and:

1. At Screening visit, have 2 bilateral buttocks with each buttock having:
 - a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS)
 - b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS)
2. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
 - a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS)
 - b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS)

A complete list of the inclusion and exclusion criteria is provided in the COA dossiers and clinical study protocols.

Reviewer's comment(s): *In Study EN3835-302, 423 subjects were included, while in Study EN3835-303, 422 subjects were included. Subjects were randomized 1:1 to receive either CCH or placebo.*

³ Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: part I. Pathophysiology. Journal of the American Academy of Dermatology. 2010 Mar 1;62(3):361-70.

2.2 Clinical Trial Design

Studies EN3835-302 and EN3835-303 were both phase 3, randomized, double-blind, placebo-controlled trials. The primary endpoint was assessed at Day 71. The following figures summarize the design (Figure 1) and assessment schedule (Figure 2).

Figure 1. Study design for Studies EN3835-302 and EN3835-303

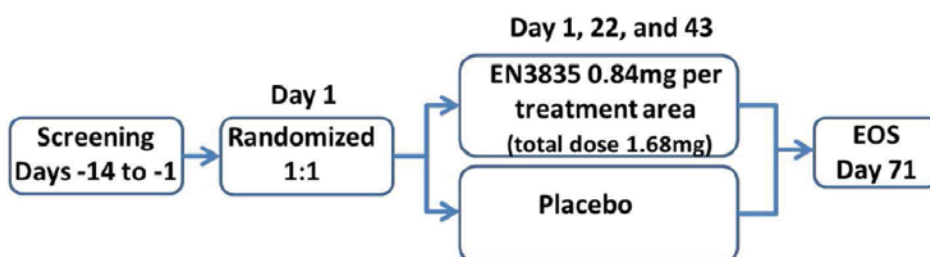
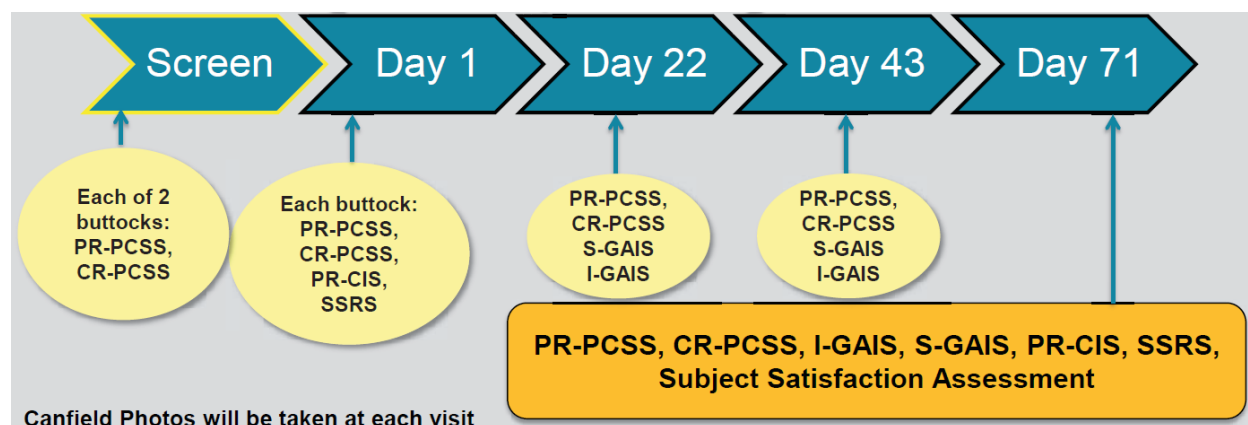


Figure 2. Assessment schedule for Studies EN3835-302 and EN3835-303



Reviewer's comment(s): Eligible subjects were randomized in a 1:1 ratio stratified by site to CCH or placebo. Subjects had up to 3 treatment sessions 21 days apart (Days 1, 22, and 43). Prior to treatment, one buttock (right or left) was randomly selected in a blind manner as the target buttock.

2.3 Endpoint Position and Definition

Table 2 describes the intended placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Studies EN3835-302 and EN3835-303.

Table 2. Endpoint model for Studies EN3835-302 and EN3835-303

Endpoint		Clinical Outcome Assessment Tool
Primary		
The proportion of 2-level composite responders at Day 71 defined as subjects with an improvement in severity from Baseline (Day 1 Visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the investigator of the target buttock <u>and</u> an improvement in severity from Baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock		CR-PCSS and PR-PCSS
Key Secondary		
Family #1	The proportion of 1-level PR-PCSS responders defined as subjects with ≥ 1 -level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1	PR-PCSS
	The proportion of 2-level PR-PCSS responders defined as subjects with ≥ 2 -level improvement in PR-PCSS severity rating of target buttock at Day 71 compared to Day 1	PR-PCSS
	The proportion of 1-level composite responders of target buttock (defined as subjects with an improvement in severity from Baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the investigator and an improvement of severity from Baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1	CR-PCSS and PR-PCSS
	The proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from Baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the investigator and an improvement of severity from Baseline of at least 1 level of severity in the PR-PCSS of the non-target buttock) at Day 71 compared to Day 1	CR-PCSS and PR-PCSS
Family #2	The proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4)	SSRS
	Change from Baseline (Day 1) of the PR-CIS total score at Day 71	PR-CIS
Family #3	The proportion of 1-level S-GAIS responders defined as subjects with ≥ 1 -level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71	S-GAIS
	Proportion of 2-level S-GAIS responders defined as subjects with ≥ 2 -level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71	S-GAIS

Abbreviations: CR-PCSS = Clinician Reported Photonumeric Cellulite Severity Scale; PR-CIS = Patient Reported Cellulite Impact Scale; PR-PCSS = Patient Reported Photonumeric Cellulite Severity Scale; S-GAIS = Subject Global Aesthetic Improvement Scale; SSRS = Subject Self-Rating Scale

Reviewer's comment(s): The primary and key secondary objectives were tested using a multiple testing approach to provide control of the familywise error rate (for the primary and key secondary tests) at a two-sided 0.05 alpha level (or, equivalently, one-sided 0.025 alpha level). Results from the multiple endpoint testing can be found in the clinical and statistical reviews.

The Subject Satisfaction with Cellulite Treatment Assessment and the Investigator Global Aesthetic Improvement Scale were used in the trials but were not specified in the statistical hierarchy as secondary endpoints or used descriptively in the product labeling and therefore are not further discussed in this review.

2.4 Labeling or promotional claims based on the COA

The following table is from the applicant's proposed labeling. The results are from the pooled data from pivotal phase 3 studies for the two co-primary composite endpoints (PR-PCSS and CR-PCSS).

(b) (4)



The Applicant has proposed specific targeted COA-related labeling claims:

1. The following draft label claim, based on the PR-PCSS and the CR-PCSS in Phase 3 study results, is intended for inclusion in the CLINICAL STUDIES section of the US prescribing information:

(b) (4)



Reviewer's comment(s): Based on the submitted data from the Applicant, the PR-PCSS and the CR-PCSS are relevant concepts. Further, the psychometric data supports that both instruments are well-defined and reliable. As such, both instruments appear to be adequate to support the proposed labeling claims.

(b) (4)



3 CONCEPTUAL FRAMEWORK

The conceptual frameworks for the COAs are shown below:

Figure 3. Conceptual Framework for Patient-Reported Photometric Cellulite Severity Scale (PR-PCSS)

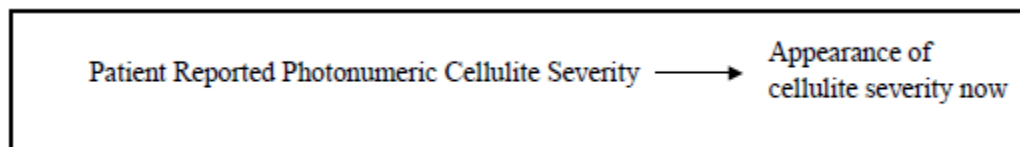


Figure 4. Conceptual Framework for Clinician-Reported Photometric Cellulite Severity Scale (CR-PCSS)

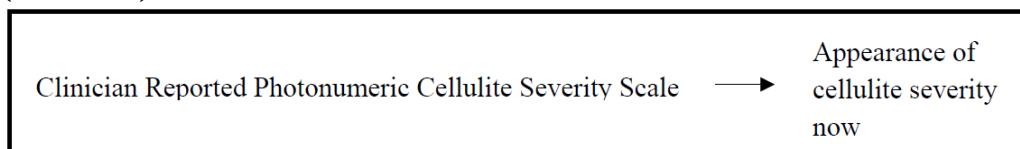


Figure 5. Conceptual Framework for the Subject Self-Rating Scale (SSRS)

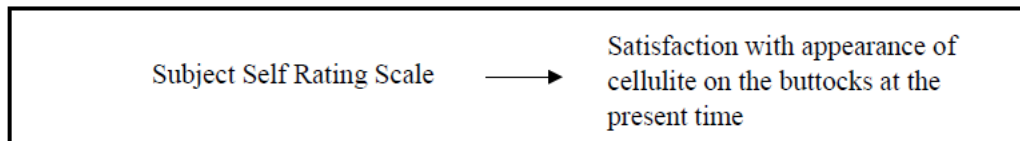


Figure 6. Conceptual Framework for the Subject Global Aesthetic Improvement Scale (S-GAIS)

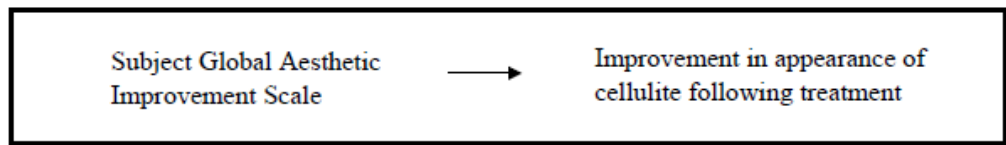
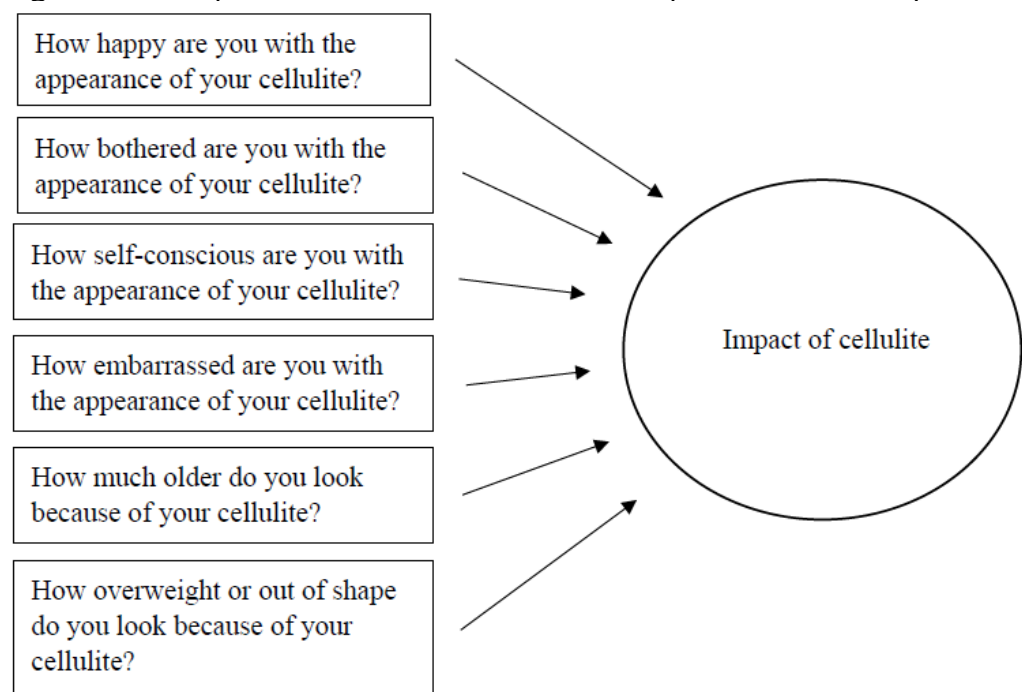


Figure 7. Conceptual Framework for the Patient-Reported Cellulite Impact Scale (PR-CIS)



4 CLINICAL OUTCOME ASSESSMENTS

Clinician-Reported Photometric Cellulite Severity Scale (CR-PCSS)

The CR-PCSS is a single-item clinician reported outcome instrument (ClinRO) with photo and written descriptions to assess the severity of cellulite (Appendix A). Two versions were developed, a version for the buttock and a version for the thigh. The recall period is momentary (i.e., clinicians will rate the respective region based on live assessment and photographs at the current study visit).

Patient-Reported Photometric Cellulite Severity Scale (PR-PCSS)

The PR-PCSS is a patient-reported outcome instrument (PRO) with photos and written descriptions to help patients self-assess the severity of cellulite (Appendix B). Two versions were developed, a version for the buttock and a version for the thigh. The recall period is momentary (i.e., subjects will rate their respective region based on photographs at the current study visit).

Subject Global Assessment of Aesthetic Improvement Scale (S-GAIS)

The S-GAIS is designed to assess the patient’s perspective of cellulite appearance after treatment. The scale has seven response options varying from “-3” (Very Much Worse) to “+3”

(Very Much Improved). Subjects are instructed to answer the following question: “*How would you rate the appearance of your treated cellulite after treatment?*” The recall period calls for the subject to compare their current state with an earlier period.

Subject Self-Rating Scale (SSRS)

The SSRS is a static, 7-level rating PRO scale ranging from 0 (Extremely dissatisfied) to 6 (Extremely satisfied) for the assessment of appearance of cellulite on the buttocks. The scale has two formats, one administered at the beginning of treatment and one at the end of the study.

Patient Reported Cellulite Impact Scale (PR-CIS)

The PR-CIS is a static, 6-item PRO instrument that assesses the impacts of cellulite, including happiness, bother, self-consciousness, embarrassment, feeling older, and feeling overweight or out of shape. All six items are rated on a 0–10 numeric rating scale (NRS), with 0 being ‘Not at all’ and 10 being ‘Extremely’.

5 SCORING ALGORITHM

CR-PCSS

The scale score ranges from 0 to 4, with a higher score indicating greater severity as determined by both number of dimples due to cellulite and depth of cellulite presentation.

PR-PCSS

The scale score ranges from 0 to 4, with a higher score indicating greater severity as determined by both the number and depth of cellulite dimples.

S-GAIS

The scale score ranges from -3 to +3, with a higher score indicating greater improvement in perceived appearance of treated cellulite.

SSRS

The scale is scored from 0 to 6 with a higher score indicating greater satisfaction in the appearance of cellulite.

PR-CIS

The scale score ranges from 0 to 60, with a higher score indicating greater (negative) impacts of cellulite. Item 1 (happiness) is reverse scored as the wording of the item is positive, while the remaining items for bother, self-conscious, embarrassment, feeling older, and feeling overweight or out of shape are negative words. If scores on two or less of the six items are missing, the PR-CIS total score is computed as the mean of the answered items multiplied by six. If scores on three or more of the six items (50%) are missing, then the PR-CIS total score is set to missing.

6 CONTENT VALIDITY

The sponsor appears to have established reasonable content validity of the CR-PCSS and PR-PCSS. Refer to previous COA consult reviews for details of the two qualitative studies conducted to evaluate the content validity of the instruments, including the results.

To date, the following information has been submitted (check all that apply):

- ☒ Copy of instrument
- ☒ Literature review and/or publications
- ☒ Documentation of expert input
- ☒ Qualitative study protocols and interview guides for focus group or patient interviews
- ☒ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☒ Synopsis of qualitative findings
- ☒ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- ☒ Quantitative summary report with evidence to support item retention and scoring
- ☒ Transcripts (if available)

Tables 4 to 7 document the adequacy of the content of the COAs.

Table 4. Review of Content Validity for CR-PCSS and PR-PCSS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☒ Literature ☒ Clinical input e.g. discussion with clinical reviewer	<i>Page 24 of ClinRO Dossier for CR-PCSS</i> <i>Page 24 of PRO Dossier for PR-PCSS</i>
Content validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☒ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☒ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☒ Response options appropriate for the item stems (measure the same	<i>Pages 24-37 of ClinRO Dossier for CR-PCSS</i> <i>Pages 24-37 of PRO Dossier for PR-PCSS</i>

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
		dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☒ Descriptive statistics (if available) support content relevance ☒ Other (see Reviewer's comments)	

The qualitative research for the PR-PCSS included two phases: concept elicitation interviews with 24 subjects and cognitive debriefing interviews with 23 subjects with cellulite. Key criteria for the qualitative research included: female ≥ 21 years of age and ≤ 60 years of age; at least one well-defined EFP dimple within the posterolateral thigh(s) and/or buttock(s) that was evident when standing; and a body mass index (BMI) between 20 and 33 kg/m².

Overall, the mean age of subjects was 40.0 years (SD=9.0), scores on the Fitzpatrick Skin type (for skin complexion) ranged from I to VI with the most frequently reported being III (n=15, 31.9%), II (n=14, 29.8%), and IV (n=11, 23.4%). The location of cellulite was most commonly reported as both the thigh and buttocks (n=34, 71.3%). Subjects had, or were diagnosed with, cellulite for an average of 12.2 years (SD=8.6).

Concept elicitation interviews:

- o When asked to describe the severity of their cellulite, they rated their condition as mild (n=3, 13%), moderate (n=6, 25%), mild-to-moderate (n=2, 8%), and severe (n=3, 13%). The remaining subjects (n=10, 46%) described their cellulite severity using terms such as “getting worse”, “pretty bad”, “extreme”, “medium”, “not severe at all”, and “not terrible”.
- o Subjects were asked to describe what improvement in cellulite meant to them, and most subjects reported that having smoother skin (n=13, 54%) and less dimpling (n=9, 38%) would indicate improvement. Subjects were also probed on what worsening in cellulite appearance meant to them. Most subjects reported that a worsening in appearance to them meant more dimpling (n=10, 42%), cellulite covering a larger area of the skin than previously (n=8, 33%), and an increased depth of dimples (n=7, 29%).
- o For the ordering exercise, over 90% of the women placed the buttock photographs in the correct order (n=22 of 24) without additional verbal cues from the labels or descriptors. Subjects used concepts related to number and depth of dimples, as well as the amount of area covered, to describe why they placed the photos in the order that they did. Subjects demonstrated an understanding of the continuum of cellulite severity portrayed in the photos and were able to provide a self-rating of their own cellulite based on the presentation of the photos. Subjects were then presented with index cards with the PR-PCSS labels on them ranging from NONE to SEVERE and were asked whether these

labels were appropriate to be attached to the buttock photos. Overall, the subjects reported that the labels fit well with the photos. Subjects expressed that the descriptors were accurate and appropriately matched both the severity labels and the photos. Overall, the subjects reported that the descriptors were easy to understand and helped clarify what the labels mean. Specifically, the subjects expressed that “deep”, “dimples”, and “superficial” were especially good words to use.

Cognitive debriefing interviews:

- o Nineteen of the 23 women (83%) were able to order the descriptors correctly in the absence of the photos and labels.
- o Feedback included the scale was “self-explanatory”, “straightforward”, and “easy to understand” (n=7, 30%) or “simple” and “clear” (n=2, 9%). All women (n=23) were able to rate themselves in terms of where they fell on the continuum of cellulite severity and indicated that five response options were an acceptable number and easy to understand and select from.
- o When reviewing the photo assigned to NONE, all subjects (100%) reported that they did not observe cellulite in the photo; specific responses included: “smooth”, “no cellulite”, “firm skin”, “no dimples or ridges”, and “tight skin”. Most subjects (n=19/21, 90%) reported that the photo was appropriate and an accurate representation of the response option label and descriptor.
- o Most subjects (greater than 80%) agreed that the photos were appropriate for representation of the response option label and descriptor. The description for Severe—A lot of dimples or ridges of which many are deep—was changed to Severe—A lot of dimples or edges of which many are deep covering most of the skin area—based on feedback that using “many” and “a lot” were too similar and that the additional differentiation of the depth of the dimples and the area of coverage with the SEVERE descriptor made the ordering of the descriptors clear.

The qualitative research for the CR-PCSS involved two studies (n=12 and n=5) with one-on-one qualitative interviews with clinicians experienced in treating cellulite. Clinicians were either specialized in dermatology or cosmetic surgery with a mean (SD) of 21.1 (12.1) years of practice.

Concept elicitation interviews:

- o Overall the majority of clinicians refer to cellulite as “dimples” or “dimpling” (n=11, 91.7%) with the majority of the clinicians using this term spontaneously (n=8, 66.7%).
- o Overall, clinicians reported assessing cellulite severity based on the number of dimples (n=10, 83.3%), depth of the dimples (n=7, 58.3%), and the area of involvement and density (n=6, 50.0%).
- o Consistent lighting was considered necessary to provide consistent shadowing to increase the reliability of the assessment of the depth of the dimples.
- o All clinicians (n=12, 100%) placed five cellulite photos in the order: None, Almost None, Mild, Moderate, and Severe.

Cognitive debriefing interviews:

- o Half of the clinicians (n=6, 50.0%) felt that the CR-PCSS was clear without instructions. The other clinicians (n=6, 50.0%) recommended adding instructions or investigator training with most suggesting information on how to standardize the assessment of the patient and the lighting in the room.
- o A total of 11 clinicians (91.7%) were asked about the quality of the photos in the CR-PCSS. The majority, eight clinicians (66.7%), provided positive endorsement on the photo quality. Three clinicians (25.0%) provided a positive endorsement on the photo quality but recommended changes such as zooming out on the location to view a larger area (two clinicians) and improvements in the lighting (one clinician).
- o After the first seven clinician interviews, the descriptors were revised to have more detailed response options by anchoring them with number of dimples and depth size. However, after the revisions, some of the clinicians indicated that quantifying the descriptors would not be desirable and the depth of the dimples from the photographs would be subjective. The Division also echoed this input. Therefore, the range of number of dimples and depth size were removed from the descriptors and more descriptive wording regarding the depth were added. During the second round of interviews, most clinicians indicated that the response option and descriptors were appropriate. Thus, no other changes were made to the instrument.

Reviewer's comment(s): *The Applicant appears to have established reasonable content validity of the CR-PCSS and PR-PCSS. Refer to previous COA consult reviews for details on COA responses to the two qualitative studies conducted to evaluate the content validity of these instruments.*

Table 5. Review of Content Validity for SSRS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☒ Literature ☐ Clinical input e.g. discussion with clinical reviewer	Page 27 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS
Content validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☒ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the	Page 28-53 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
		target patient population ☒ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☒ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☒ Descriptive statistics (if available) support content relevance ☒ Other (see Reviewer's comments)	

Reviewer's comment(s): The SSRS was added to the other two instruments (PR-CIS and S-GAIS) and all four measures were tested in cognitive interviews (n=20) (study 22641).

For the SSRS, subjects in the cognitive interviews found the item and response options to be clear and easy to answer. A few individuals were confused with reference to the clinical trial wording of the item (i.e., treatment name, Day 71); however, that was due to the participants not being enrolled in an actual clinical trial. On face, evaluating satisfaction of the appearance of cellulite is appropriate.

Table 6. Review of Content Validity for S-GIAS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☐ Yes ☒ No	☒ Literature ☐ Clinical input e.g. discussion with clinical reviewer	Page 27 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS
Content validity	☐ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☒ No	☐ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☐ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative	Page 28-53 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
		research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☒ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☒ Other (see Reviewer's comments)	

Reviewer's comment(s): *In the IND phase, the Applicant was advised that the Agency views the S-GAIS as an exploratory measure that can be used as an anchor for determining what constitutes a clinically meaningful within-patient change in other study endpoints. This particular scale is susceptible to recall error due to the recall period and will not be able to allow change from baseline analyses.* (b) (4)

(b) (4). *The Applicant had inquired whether they could anchor the PR-PCSS to the S-GAIS to support the use of the PR-PCSS as a secondary endpoint. The Division had previously communicated to the Applicant that they would need to anchor the PR-PCSS to a 2-point change on the S-GAIS to give them greater confidence in the change needed on the PR-PCSS.*

The S-GAIS was tested in combined concept elicitation and cognitive interviews (n=15) followed by separate cognitive interviews with a different sample (n=12) (study 11718-001). The S-GAIS and the PR-CIS were tested in additional combined concept elicitation and cognitive interviews (n=17) (study 11718-004). The SSRS was then added and all four measures were tested in cognitive interviews (n=20) (study 22641).

(b) (4)

Table 7. Review of Content Validity for PR-CIS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☐ Yes ☒ No	☒ Literature ☐ Clinical input e.g. discussion with clinical reviewer	Page 27 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS
Content validity	☐ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☒ No	☐ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☐ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☒ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☒ Other (see Reviewer's comments)	Page 28-53 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS

Reviewer's comment(s): The S-GAIS and the PR-CIS were tested in additional combined concept elicitation and cognitive interviews (n=17) (study 11718-004). The SSRS was then added and all four measures were tested in cognitive interviews (n=20) (study 22641).

On face, for the PR-CIS, there are some questions (i.e., asking patients about how much older they look, how overweight they look) that may be misleading if taken out of context. The drug is specifically for the treatment of cellulite in adult women, not for helping patients to look younger or less overweight. During the cognitive interviews (in study 11718-004), some subjects indicated that for the PR-CIS they found question 5 (n=4; looking older due to cellulite) and question 6 (n=4; looking overweight) irrelevant. Participants found that the questions not

important to ask someone with cellulite. Some subjects interpreted items as relating to satisfaction with the treatment, rather than specifically relating to the appearance of their cellulite as intended (three subjects for item 1 and one subject for item 2). Similarly, in study 22641, some participants (n=4) indicated confusion with question 5 and the association between age and the cellulite. The subjects associated looking old as in their overall look (not specific to their cellulite).

(b) (4)

7 OTHER MEASUREMENT PROPERTIES

To date, the following information has been submitted (check all that apply):

- ☒ Literature review and/or publications
- ☒ Quantitative analysis synopsis
- ☒ Full quantitative analysis plan
- ☒ Quantitative summary report with evidence to support reliability, construct validity, ability to detect change and scoring

The quantitative analysis plan is adequate and includes details on the following:

- ☒ Pre-specified hypothesized relationships among variables to be tested
- ☒ Pre-specified estimates for reliability
- ☒ Appropriate anchors (e.g., global scales) for evaluation of meaningful change.

Tables 11 and 12 document the adequacy of the other measurement properties of the CR-PCSS and PR-PCSS, and the SSRS, respectively.

Table 11. Review of Other Measurement Properties for CR-PCSS and PR-PCSS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC ≥ 0.70) ☒ Inter-rater reliability estimates in acceptable range (for CR-PCSS only) ☐ Other (see Reviewer's comments)	<i>Page 38-48 of ClinRO Dossier for CR-PCSS</i> <i>Pages 38-40 of PRO Dossier for PR-PCSS</i>
Construct validity	☒ Yes ☐ Potentially – insufficient evidence available; additional	☒ Relationship to other assessments with similar concepts is as expected ☒ Relationship to other assessments with dissimilar concepts is as expected	<i>Page 49-52 of ClinRO Dossier for CR-PCSS</i>

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
	information is needed ☐ No	☐ COA differentiates between clinically distinct groups (i.e., known groups validity) ☐ COA scores are related to a known gold standard assessment of the same concept ☒ Other (see Reviewer's comments)	<i>Pages 41-44 of PRO Dossier for PR-PCSS</i>
Ability to detect change	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept ☒ Other (see Reviewer's comments)	<i>Page 52-53 of ClinRO Dossier for CR-PCSS</i> <i>Page 44 of PRO Dossier for PR-PCSS</i>

Reviewer's comment(s): From COA perspective, the evidence submitted on the reliability and validity in both CR-PCSS and PR-PCSS (see previous COA reviews) appeared sufficient to support their use for endpoint evaluation.

- o For the PR-PCSS, the test-retest reliability analysis demonstrated substantial agreement in ratings for the left and right buttock. The ICC was 0.87 (95% CI: 0.813, 0.911) and 0.86 (95% CI: 0.794, 0.901) for the left and right buttock, respectively.
- o For the CR-PCSS, Study EN3835-302 assessed the test-retest reliability of the CR-PCSS at two assessment time points, 14 days apart, by viewing 100 digital images. All intra-rater reliability estimates were >0.80 . Inter-rater reliability estimates for both assessment time points also were all >0.80 . Study EN3835-303 evaluated the test-retest reliability of the CR-PCSS in live subjects. Intra-rater intraclass correlation coefficients (ICC) for consistency and agreement for the left buttock ranged from 0.71 to 0.91 and 0.69 to 0.91, respectively. For the right buttock the ICCs ranged from 0.74 to 0.92 and 0.70 to 0.92, respectively. Inter-rater reliability estimates were ≥ 0.70 for the left and right buttocks.
- o To demonstrate convergent validity, a moderate association (0.49) between the PR-PCSS and the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) was observed at Day 71. Moderate to large correlations were observed between the PR-PCSS and Subject Self-Rating Scale (SSRS) and Patient Reported Cellulite Impact Scale (PR-CIS) ($r = -0.57$ and 0.48 , respectively).
- o In support of responsiveness, the correlation between change in the CR-PCSS and the Investigator Global Aesthetic Improvement Scale (I-GAIS) was strong ($r = -0.65$).
- o For the responsiveness of the PR-PCSS, correlations between change in the PR-PCSS and changes in the SSRS, SSCTA, and S-GAIS were strong ($r = -0.50$, -0.55 , and -0.58 , respectively) while correlation with changes in the PR-CIS total score was moderate ($r = 0.44$).

Table 12. Review of Other Measurement Properties for SSRS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC ≥ 0.70) ☐ Inter-rater reliability estimates in acceptable range ☒ Other (see Reviewer’s comments)	Page 54-62 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS
Construct validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Relationship to other assessments with similar concepts is as expected ☒ Relationship to other assessments with dissimilar concepts is as expected ☐ COA differentiates between clinically distinct groups (i.e., known groups validity) ☐ COA scores are related to a known gold standard assessment of the same concept ☒ Other (see Reviewer’s comments)	Page 63-65 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS
Ability to detect change	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept ☒ Other (see Reviewer’s comments)	Page 64-66 of Other PRO Dossier for S-GIAS, PR-CIS, and SSRS

Reviewer’s comment(s): A stand-alone, non-interventional study was designed to evaluate the test-retest reliability of the SSRS, PR-CIS, and S-GAIS. For all instruments, the ICC was ≥ 0.70 .

Construct validity and responsiveness were assessed using data from the EN3835-302 and EN3835-303 clinical studies. For convergent validity, a strong association (-0.50) was observed between the SSRS and PR-CIS. Correlations of the SSRS and PR-CIS with the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) were weak at Baseline, but strong at Day 71 (-0.57 and 0.48, respectively).

For responsiveness, correlations between changes in the SSRS and S-GAIS and change in the PR-PCSS were strong ($r = -0.50$ and -0.58 , respectively) while correlation with changes in the PR-CIS and PR-PCSS was moderate ($r = 0.44$).

The evidence provided for the measurement properties of the SSRS was adequate.

Review of Other Measurement Properties of the S-GAIS and PR-CIS:

To note, testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity. Therefore, while the S-GAIS and PR-CIS may show some adequate measurement properties, the content validity of the instruments was not sufficiently established.

8 INTERPRETATION OF SCORES

For the CR-PCSS and PR-PCSS, to date, the following information has been submitted (check all that apply):

- ☒ Anchor-based analyses
- ☒ Anchor-based empirical cumulative distribution function (eCDF) curves
- ☒ Anchor-based probability density function (PDF) curves
- ☒ Qualitative support for meaningful change (e.g., patient input)

Table 13 documents the adequacy of the score interpretability of the CR-PCSS and PR-PCSS.

Table 13. Review of Score Interpretability for CR-PCSS and PR-PCSS in Studies EN3835-302 and EN3835-303

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Appropriate global anchor scales were included for anchor-based analyses ☒ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☒ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☒ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☒ Other (see Reviewer’s comments)	<i>Page 54-57 of ClinRO Dossier for CR-PCSS</i> <i>Page 45-50 of PRO Dossier for PR-PCSS</i>

Reviewer’s comment(s): *The Division had previously communicated to the Applicant that they would need to anchor the CR-PCSS and PR-PCSS to a 2-point change on the GAIS to give them greater confidence in the change needed on the instruments.*

As seen in Table 14, based on a 1-level improvement in S-GAIS (“improved”), the PR-PCSS meaningful change threshold is 0.94 points (~1 level rating change). Based on a 2-level change

in S-GAIS (“much improved”), the PR-PCSS meaningful change threshold is 1.45 points. Effect sizes are all statistically large at -1.89 and -2.89, respectively.

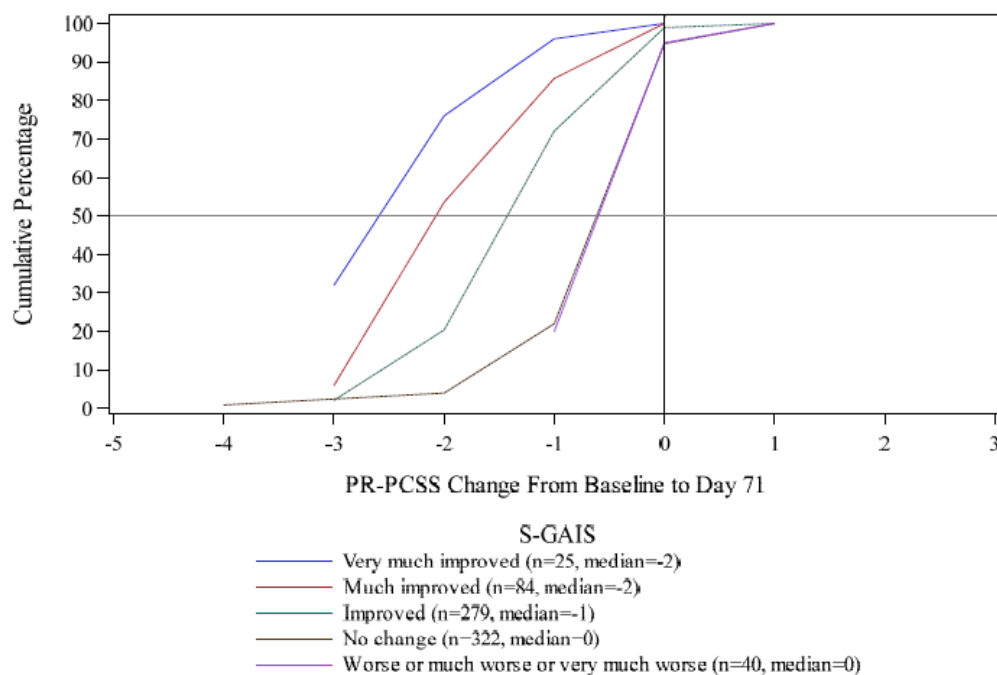
As seen in Table 15, based on a 1-level improvement in I-GAIS (“improved”), the CR-PCSS meaningful-change threshold is 0.75 points. Based on a 2-level improvement in I-GAIS (“much improved”), CR-PCSS meaningful-change threshold is 1.45. Effect sizes are large at -1.55 and -3.11, respectively.

Secondary endpoints generally should be supportive of the primary endpoint, therefore, again, it was recommended to anchor the S-GAIS to a 2-point change on the PR-PCSS and CR-PCSS. Based on the CDF plots (Figures 8 and 9; at the median line), the “Much/Very Much Improved” S-GAIS anchor categories represent a 2-point change on the instruments which equates to at least a 2-point change in the S-GAIS.

Table 14. Meaningful Change Thresholds for PR-PCSS by S-GAIS Group – Target Buttock in Studies EN3835-302 and EN3835-303 Pooled Treatment of CCH and Placebo

	N	Day 1 Mean (SD)	Day 71 Mean (SD)	Change Mean (SD)	% Change from Baseline	Effect Size	
S-GAIS at Day 71							262.9 (<0.0001)
+3 Very much improved	25	3.40 (0.50)	1.36 (0.76)	-2.04 (0.84)	60.0%	-4.08	
+2 Much improved	84	3.50 (0.50)	2.05 (0.81)	-1.45 (0.81)	41.4%	-2.89	
+1 Improved	279	3.57 (0.50)	2.63 (0.77)	-0.94 (0.76)	26.3%	-1.89	
0 No change	322	3.61 (0.49)	3.38 (0.73)	-0.23 (0.68)	6.4%	-0.46	
-1, -2, -3 Worsen groups	40	3.75 (0.44)	3.60 (0.59)	-0.15 (0.48)	4.0%	-0.34	

Figure 8. Empirical Cumulative Distribution Function of PR-PCSS from Day to Day 71 by S-GAIS Group – Target Buttock in Studies EN3835-302 and EN3835-303 Pooled Treatment of CCH and Placebo



Abbreviations: PR-CSS= Patient Reported Photometric Cellulite Severity Scale; S-GAIS= Subject Global Aesthetic Improvement Scale

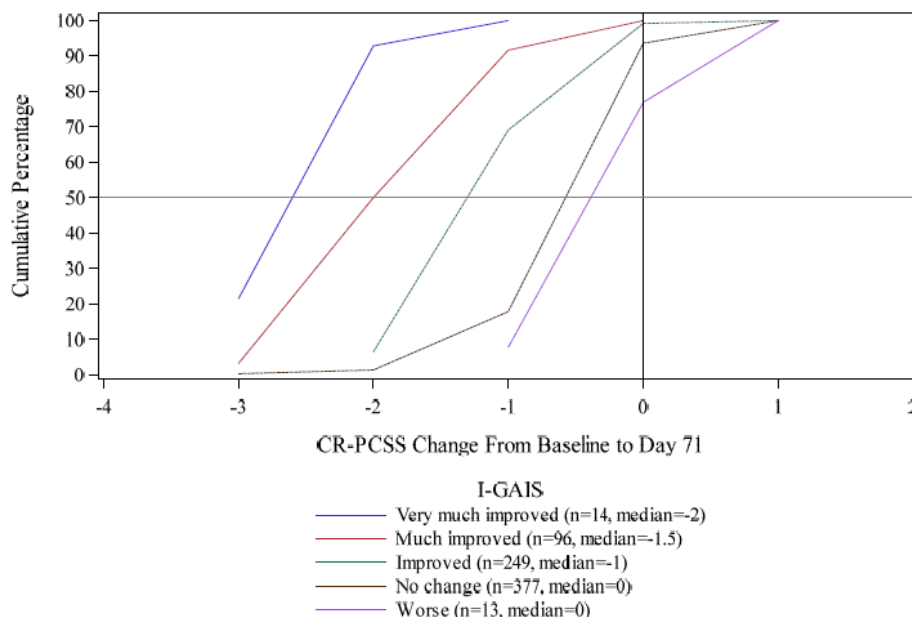
Table 15. Meaningful Change Thresholds for CR-PCSS by I-GAIS Group – Target Buttock in Studies EN3835-302 and EN3835-303 Pooled Treatment of CCH and Placebo

	N	Day 1 Mean (SD)	Day 71 Mean (SD)	Change Mean (SD)	% Change from Baseline	Effect Size	H-value ¹ (p-value)
I-GAIS at Day 71							322.8 (<0.0001)
+3 Very much improved	14	3.07 (0.27)	0.93 (0.47)	-2.14 (0.53)	69.7%	-8.02	
+2 Much improved	96	3.31 (0.47)	1.86 (0.73)	-1.45 (0.69)	43.8%	-3.11	
+1 Improved	249	3.36 (0.48)	2.61 (0.69)	-0.75 (0.58)	22.3%	-1.55	
0 No change	377	3.43 (0.50)	3.30 (0.63)	-0.13 (0.53)	3.8%	-0.26	
-1, -2, -3 Worsen groups	13	3.46 (0.52)	3.62 (0.65)	0.15 (0.55)	4.3%	0.30	

Abbreviations: I-GAIS=Investigator Global Aesthetic Improvement Scale; SD=Standard deviation

¹ Kruskal-Wallis one-way ANOVA model; ANOVA model includes I-GAIS group as the independent variable and the CR-PCSS change scores as the dependent variable

Figure 8. Empirical Cumulative Distribution Function of CR-PCSS from Day 1 to Day 71 by I-GAIS Group – Target Buttock in Studies EN3835-302 and EN3835-303 Pooled Treatment of CCH and Placebo



Abbreviations: CR-PSS=Clinician Reported Photonumeric Cellulite Severity Scale; I-GAIS=Investigator Global Aesthetic Improvement Scale

The following tables (Tables 16 and 17) are the frequency of each response option for the SSRS (at Baseline and Day 71). Table 18 is the endpoint evaluation for the frequency of 1-level responders on the SSRS (subjects who scored ≥ 4 at Day 71).

Table 16. Frequency distribution for SSRS – Baseline in Studies EN3835-302 and EN3835-303

		Study Drug	
Visit		CCH 0.84 mg/buttock	Placebo
SSRS rating	Statistic [2]	(N=424)	(N=419)
Baseline			
Extremely Satisfied (6)	n (%)	0 (0.0)	2 (0.5)
Satisfied (5)	n (%)	3 (0.7)	2 (0.5)
Slightly Satisfied (4)	n (%)	7 (1.7)	10 (2.4)
Neither Satisfied nor Dissatisfied (3)	n (%)	10 (2.4)	5 (1.2)
Slightly Dissatisfied (2)	n (%)	37 (8.7)	30 (7.2)
Dissatisfied (1)	n (%)	133 (31.4)	143 (34.2)
Extremely Dissatisfied (0)	n (%)	234 (55.2)	226 (54.1)
Not Done	n	0	1
	Mean	0.7	0.7
	SD	0.94	0.98

Table 17. Frequency distribution for SSRS – Day 71 in Studies EN3835-302 and EN3835-303

Visit SSRS rating	Statistic [2]	Study Drug	
		CCH 0.84 mg/buttock (N=424)	Placebo (N=419)
Day 71			
Extremely Satisfied (6)	n (%)	19 (5.1)	5 (1.3)
Satisfied (5)	n (%)	80 (21.6)	27 (7.1)
Slightly Satisfied (4)	n (%)	93 (25.1)	47 (12.3)
Neither Satisfied nor Dissatisfied (3)	n (%)	56 (15.1)	76 (19.9)
Slightly Dissatisfied (2)	n (%)	31 (8.4)	49 (12.9)
Dissatisfied (1)	n (%)	61 (16.5)	85 (22.3)
Extremely Dissatisfied (0)	n (%)	30 (8.1)	92 (24.1)
Not Done	n	54	38
	Mean	3.2	2.0
	SD	1.74	1.65

Table 18. Frequency distribution for 1-level SSRS responders (subjects who scored ≥ 4 at Day 71) – Day 71 in Studies EN3835-302 and EN3835-303

One-Level SSRS Responder [2]	Statistic [3]	Study Drug		CCH 0.84 mg/buttock vs Placebo	
		CCH 0.84 mg/buttock (N=424)	Placebo (N=419)	Odds Ratio (95% CI)	p-Value [4]
Yes	n (%)	192 (45.3)	79 (18.9)	3.61 (2.64, 4.95)	<0.001
No	n (%)	232 (54.7)	340 (81.1)		

Reviewer's comment(s): After reviewing the data, the SSRS showed that patients achieved satisfaction at Day 71. Biostatistics has determined that the achievement was a robust result.

The following tables (Table 19 and 20) were populated to evaluate if any items from the PR-CIS was driving the total score and to review the changes between CCH subjects and placebo subjects.

Table 19. Change from Baseline on PR-CIS Item Scores for CCH Subjects (n=424) in Studies EN3835-302 and EN3835-303

	N	Day 1 Mean (SD)	N	Day 71 Mean (SD)	N	Change Mean (SD)
Happiness	423	1.0 (2.18)	370	4.3 (2.98)	369	3.5 (3.51)
Bothersome	423	8.4 (2.77)	370	6.4 (2.87)	369	-2.0 (3.65)
Self-Consciousness	423	8.9 (2.03)	370	6.9 (2.71)	369	-1.9 (2.75)
Embarrassment	423	8.9 (1.81)	370	6.8 (2.84)	369	-2.1 (2.79)
Old Appearance	423	7.8 (2.41)	370	6.1 (2.96)	369	-1.7 (3.07)
Overweight	423	8.7 (1.86)	370	7.1 (2.68)	369	-1.6 (2.61)
Total Score	423	51.8 (8.45)	424*	40.1 (13.30)	423	-11.7 (12.58)

*Baseline value is imputed to Day 71 for any subjects without Day 71 PR-CIS total score

Table 20. Change from Baseline on PR-CIS Item Scores for Placebo Subjects (n=419) in Studies EN3835-302 and EN3835-303

	N	Day 1 Mean (SD)	N	Day 71 Mean (SD)	N	Change Mean (SD)
Happiness	415	0.7 (1.82)	381	2.2 (2.77)	377	1.5 (3.10)
Bothersome	415	8.4 (2.88)	381	7.1 (3.20)	377	-1.3 (4.01)
Self-Consciousness	415	8.7 (2.34)	381	7.6 (2.73)	377	-1.1 (2.65)
Embarrassment	415	8.9 (2.14)	381	7.6 (2.72)	377	-1.2 (2.65)

Old Appearance	415	7.6 (2.55)	381	6.7 (3.12)	377	-1.0 (3.05)
Overweight	415	8.7 (1.87)	381	7.8 (2.48)	377	-0.9 (2.44)
Total Score	415	51.6 (9.58)	419*	45.4 (12.77)	415	-6.2 (11.67)

*Baseline value is imputed to Day 71 for any subjects without Day 71 PR-CIS total score

Reviewer's comment(s): *The PR-CIS appears to show small effects of change for each of the items (around 1-point). Also, while the "happiness" item had a slightly higher magnitude of change, the concept overlaps with satisfaction which is already reflective in the SSRS instrument.*

D. APPENDICES

Appendix A: Clinician-reported Photometric Cellulite Severity Scale (CR-PCSS)

Appendix B: Patient-reported Photometric Cellulite Severity Scale (PR-PCSS)

Appendix C: Subject Self-Rating Scale (SSRS)

Appendix D: Subject Global Aesthetic Improvement Scale (S-GAIS)

Appendix E: Patient-Reported Cellulite Impact Scale (PR-CIS)

Appendix A: Clinician-reported Photometric Cellulite Severity Scale (CR-PCSS)



Appendix B: Patient-reported Photometric Cellulite Severity Scale (PR-PCSS)



Patient Instructions for Use of the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)

Cellulite is a dermatological condition that is most evident in the buttocks and on the back of the thighs. One of the most common characteristics of cellulite is the appearance of dimples or ridges on the surface of the skin. These dimples or ridges can vary in number, the depth of the dimples or ridges, and the amount of skin area that is covered by them. People with more severe cellulite generally have a greater number of dimples, greater depth of dimples, greater number of ridges and/or a greater area of skin covered by the dimples and ridges than persons with milder cellulite.

Up to 4 digital photographic images have been taken of you, one of your left buttocks, one of your right buttocks, one of the back of your left thigh, and one of the back of your right thigh. These images will be displayed to you on a computer monitor one at a time.

After you familiarize yourself with your pictures you will be asked to rate your own cellulite displayed in these digital images by comparing the image on the monitor to a scale (based on a series of pictures) that will be on a foamboard that is given to you by a staff member. The scale contains a series of pictures, labels, and descriptions of different severity levels of cellulite. You will rate the 4 images taken of your buttocks and thighs for cellulite severity as compared to the scale, one at a time, and in random order.

The scale has 5 levels of severity, varying from no cellulite (Score=0), almost none (Score=1), mild (Score=2), moderate (Score=3), to severe cellulite (Score=4). Each severity level is accompanied by a picture which illustrates what the cellulite at that severity level may look like. Each picture on the scale has a description of the severity level to assist in your evaluation.

The severity of your cellulite in one region displayed on the monitor might be the same or it might be different than other regions; as an example the cellulite on your right thigh might be more or less severe than your right buttock. The cellulite severity in one region should not influence you in rating the severity of cellulite in another region.

Do not assume that you have cellulite in the region you will view. There may be one or more regions that you will be asked to evaluate that have no cellulite and which would be rated as a Score of 0.

Also, rate the cellulite in the image that you see at the time you are asked to do this evaluation; do not think about previously looking at your body or regions in mirrors or photos and assessing your cellulite; do not think about rating areas of your body that are not part of the image, or do not try to remember in the past what you rated your cellulite; only rate the cellulite in the photo image here and now; in the present.

This is how each level of the scale is described:

- Score=0; None
 - No evident cellulite
- Score=1; Almost None
 - A few superficial dimples or ridges
- Score=2; Mild
 - Several dimples or ridges of which most are superficial
- Score=3; Moderate
 - Many dimples or ridges of which most are somewhat deep
- Score=4; Severe
 - A lot of dimples or ridges which many are deep covering most of the skin area

You may only select whole number scores. You are not allowed to score an area a half grade; for example, you are not allowed to score a region as 2.5 because you feel that your cellulite was half-way between mild (Score=2) and moderate (Score=3); round up and select the more severe response.

Please realize that there is no right or wrong cellulite score for a region and there is no time limit for you to complete these assessments; so take your time and rate yourself for that region to the best of your ability.

Patient Reported

Photonumeric Cellulite Severity Scale (PR-PCSS) – Buttock



Produced by CANFIELD Scientific, Inc.

Version 8.0

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Appendix C: Subject Self-Rating Scale (SSRS)

Subject Self-Rating Scale (SSRS)	
Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time?	
☐ 6	Extremely satisfied
☐ 5	Satisfied
☐ 4	Slightly satisfied
☐ 3	Neither satisfied nor dissatisfied
☐ 2	Slightly dissatisfied
☐ 1	Dissatisfied
☐ 0	Extremely dissatisfied

Subject Self-Rating Scale (SSRS)	
Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with EN3835?	
☐ 6	Extremely satisfied
☐ 5	Satisfied
☐ 4	Slightly satisfied
☐ 3	Neither satisfied nor dissatisfied
☐ 2	Slightly dissatisfied
☐ 1	Dissatisfied
☐ 0	Extremely dissatisfied

Appendix D: Subject Global Aesthetic Improvement Scale (S-GAIS)

Rating	Response Option	Description
+3	Very much improved	My treated cellulite looks very much better.
+2	Much improved	My treated cellulite looks much better, but additional treatment would slightly improve the result.
+1	Improved	My treated cellulite looks better, but additional treatment is necessary.
0	No change	My treated cellulite looks essentially the same as it did originally.
-1	Worse	My treated cellulite looks worse than it did originally.
-2	Much worse	My treated cellulite looks much worse than it did originally.
-3	Very much worse	My treated cellulite looks very much worse than it did originally.

Appendix E: Patient-Reported Cellulite Impact Scale (PR-CIS)

Patient Reported Cellulite Impact Scale (PR-CIS)											
Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question.											
1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite?											
Not at all											Extremely
0	1	2	3	4	5	6	7	8	9	10	
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite?											
Not at all											Extremely
0	1	2	3	4	5	6	7	8	9	10	
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite?											
Not at all											Extremely
0	1	2	3	4	5	6	7	8	9	10	
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite?											
Not at all											Extremely
0	1	2	3	4	5	6	7	8	9	10	
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite?											
Not at all											Extremely
0	1	2	3	4	5	6	7	8	9	10	
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite?											
Not at all											Extremely
0	1	2	3	4	5	6	7	8	9	10	
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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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: May 14, 2020

To: Craig Johnson, PharmD
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: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRADENAME (collagenase clostridium histolyticum)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: BLA 761146

Applicant: Endo Global Aesthetics Limited

1 INTRODUCTION

On September 6, 2019, Endo Global Aesthetics Limited, submitted for the Agency's review an original Biologics License Application (BLA-761146) for TRADENAME (collagenase clostridium histolyticum) Injection, for subcutaneous use, for the proposed indication of treatment of moderate to severe cellulite in the buttocks of adult women.

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 January 24, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (collagenase clostridium histolyticum) Injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft TRADENAME (collagenase clostridium histolyticum) PPI received on September 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 8, 2020.
- Draft TRADENAME (collagenase clostridium histolyticum) Prescribing Information (PI) received on September 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 8, 2020.

3 REVIEW METHODS

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 PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

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

4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
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Clinical Inspection Summary

Date	May 12, 2020
From	Cheryl Grandinetti, PharmD, Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Cristina Attinello, RPM Melinda McCord, MD, Medical Reviewer Gordana Diglisic, MD, Medical Team Leader Kendall Marcus, MD, Division Director Division of Dermatology and Dentistry (DDD)
BLA #	761146
Applicant	Endo Global Aesthetics Limited
Drug	Collagenase clostridium histolyticum
NME	Yes
Proposed Indication	For the treatment of moderate to severe cellulite in the buttocks of adult women
Consultation Request Date	22 October 2019
Summary Goal Date	20 June 2020
Action Goal Date	20 Aug 2020
PDUFA Date	6 Sep 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Bank, Schlessinger, Coleman, and Gold were inspected in support of this BLA (761146). The inspections covered Protocols EN3835-302 and EN3835-303.

Underreporting of an adverse events of special interest was noted during the inspections of Drs. Bank and Schlessinger for Protocol EN3835-302. Specifically, cases of bruising at the injection site in the left and/or right buttocks occurred in 5 subjects (Subject #s (b) (6)). Details regarding these cases are described further in Section III. These additional unreported cases of bruising should be noted in the review division's safety review.

Notwithstanding this observation, the studies appear to have been conducted adequately, and the data, including the primary efficacy endpoint data for the two protocols (EN3835-302 and EN3835-303) otherwise appear acceptable in support of the respective indication.

II. BACKGROUND

This application was submitted in support of the use of the use of collagenase clostridium histolyticum (CCH) for the treatment of edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite.

The key studies supporting the application were the following:

- EN3835-302, “A Phase 3, Randomized, Double-blind, Placebo-controlled Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy”
- EN3835-303, “A Phase 3, Randomized, Double-blind, Placebo-controlled Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy”

Protocol Number: EN3835-302

- *Subjects:* A total of 423 subjects received at least 1 dose of study drug (210 in the CCH treatment group and 213 in the placebo treatment group)
- *Sites:* 26 sites in the US
- *Study Initiation and Completion Dates:* 05 Feb 2018 to 26 Sep 2018

Protocol Number: EN3835-303

- *Subjects:* A total of 422 subjects enrolled in the study; 420 subjects received at least 1 dose of study drug (214 in the CCH treatment group and 206 in the placebo treatment group)
- *Sites:* 25 sites in the US
- *Study Initiation and Completion Dates:* 08 Feb 2018 to 26 Sep 2018

Protocols EN3835-302 and EN3835-303

Both protocols were identical in study design, and were Phase 3, multicenter, randomized, double-blind, placebo-controlled studies comparing CCH to placebo in adult women with EFP. The primary objective was to assess the efficacy and safety of CCH in the treatment of EFP in adult women.

The studies consisted of a Screening Visit (Day -14 to Day -1), Treatment Visit 1 (Day 1), Treatment Visit 2 (Day 22), Treatment Visit 3 (Day 43), and End of Study or Early Termination Visit (Day 71). Subjects meeting the entry criteria for this study were randomized (in a 1:1 ratio) via an Interactive Web Response System (IWRS) to the following:

- CCH treatment injections (1.68 mg/7.2 mL total dose) on Days 1, 22, and 43.
- Placebo treatment injections (7.2 mL total volume) on Days 1, 22, and 43

In addition, one buttock was randomly assigned by the IWRS as the target buttock for the primary efficacy endpoint (although both buttocks were treated). Subjects, investigators, site personnel, and sponsor personnel were blinded to the identification of the target buttock. Selection of dimples to be treated in the buttocks was at the discretion of the Investigator. Each treatment visit consisted of 12 injections (CCH 0.07 mg/0.3 mL or 0.3 mL placebo per injection) in each of the two buttocks for a total of 24 injections and a total volume of 7.2 mL (CCH 1.68 mg or placebo).

Each buttock was to receive the 24 injections at Days 1, 22 and 43 treatment visits unless the buttock was dimple-free (i.e., had no treatable EFP dimples and the Investigator rated the buttock a score of 0 on the CR-PCSS at Treatment Visit 2 or Treatment Visit 3). If no injections in a buttock (right or left) were given at Treatment Visit 2, subjects were assessed for treatment in the contralateral buttock at Treatment Visit 2 and returned for the Day 43 visit. Each of the buttocks was again evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS) at the Day 43 visit. If the Investigator rated either or both buttocks greater than 0 on the CR-PCSS, injections at Treatment Visit 3 should have been given. End of study was on Day 71.

The *primary efficacy endpoint* was the proportion of 2-level composite responders at Day 71, defined as subjects with at least one of two treated buttocks with:

- An improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) as assessed live by the Investigator, AND
- An improvement in severity from baseline of at least 2 levels of severity in the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) as assessed by the subject while viewing the digital image of the same buttock

A subject was considered a responder if the above criteria were met in the randomized target buttock of that subject.

At every treatment visit, each of the buttocks was photographed both before and after marking dimples and injection sites on the subject's buttocks. The subject was to assess the pre-marking digital photographic image of each of the buttocks using the PR-PCSS to determine the severity of EFP in each of the buttocks. Subsequently, the Investigator conducted live assessments of each buttock using the CR-PCSS. The subject assessments were to be completed before and independently of the Investigator assessments at each treatment visit. All the assessments must have been done before the dimple marking.

The subject assessments were done using a subject-assigned password protected electronic patient reported outcome (ePRO) system, and the Investigator and study site personnel were not to have access to the subject's assessments or password. The clinician-reported outcome (ClinRO) assessments were recorded in an investigator-assigned password protected system, and the subjects were not to have access to the Investigator's assessments or password. Subject assessments were to be done alone with no study site personnel in the room.

Investigators were instructed not to verbalize their ratings while in the presence of the subject.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, and prior inspectional history.

III. RESULTS (by site):

1. David Bank, M.D.
Protocol EN3835-302
Site #1348
359 East Main Street Suite 4G
Mount Kisco, NY 10549
Inspection Dates: 2 to 5 December 2019

At this site for Protocol EN3835-302, 17 subjects were screened, 14 were enrolled, 13 completed the study, and 1 subject withdrew informed consent. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, source data and records, electronic case report forms (eCRFs), electronic clinical outcome assessment (eCOA) primary efficacy endpoint data (i.e., PR-PCSS and CR-PCSS), drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all 17 subjects who were screened was conducted.

One adverse event was observed during the inspection that was not reported to the sponsor. Specifically, subject # (b) (6) (randomized to placebo/left buttock) experienced mild bruising at the injection site. The left or right buttock not specified. This adverse event of special interest occurred on (b) (6) and resolved on (b) (6).

Reviewer's comment: This adverse event of special interest was not found in the sponsor's data listings and should be noted in the safety review.

The source records for the primary efficacy endpoint data were reviewed and verified against the data listings provided by the sponsor for all 14 subjects enrolled; no discrepancies were noted.

2. Joel Schlessinger, M.D.
Protocol EN3835-302
Site #1370
2802 Oak View Drive
Omaha, NE 68144
Inspection Dates: 9-12 December 2019

At this site for Protocol EN3835-302, 35 subjects were screened, 31 were enrolled, 30 completed the study, and 1 subject was lost to follow-up. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, source data and records, eCRFs, eCOA primary efficacy endpoint data (i.e., PR-PCSS and CR-PCSS), drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. For the 31 subjects who were enrolled, an audit was conducted for 100% of the subjects' informed consent, eligibility criteria, and drug dispensing records; 58% of eCRFs, AE reporting, and protocol deviations; and 68% of subjects source laboratory records.

The following unreported *adverse event of special interest* for 4 subjects were observed during inspection and listed in Table 1 below.

Table 1: Unreported adverse events of special interest for Site #1370

Subject Number (randomization)	AESI	Date Occurred	Date Resolved	Severity
(b) (6) (CCH 1.68 mg/Left buttock)	Bruising on left buttock	(b) (6)	(b) (6)	Mild
(b) (6) (CCH 1.68 mg/Left buttock)	Bruising on right buttock			Mild
(b) (6) (CCH 1.68 mg/Left buttock)	Bruising on left buttock			Mild
(b) (6) (CCH 1.68 mg/Left buttock)	Bruising on right buttock			Mild
(b) (6) (CCH 1.68 mg/Right buttock)	Bruising on left buttock			Mild
(b) (6) (CCH 1.68 mg/Right buttock)	Bruising on right buttock			Mild
(b) (6) (CCH 1.68 mg/Right buttock)	Bruising on left buttock			Mild
(b) (6) (CCH 1.68 mg/Right buttock)	Bruising on right buttock			Mild

Reviewer's comment: These adverse events of special interest were not found in the sponsor's data listings and should be noted in the review division's safety review. These unreported adverse events of special interest were discussed with Dr. Schlessinger during the inspection close-out meeting. He acknowledged the unreported AEs and promised to make improvements in the future.

The source records for the primary efficacy endpoint data were reviewed and verified against the data listings provided by the sponsor for all 31 subjects enrolled; no discrepancies were noted.

3. William Coleman, III, M.D.
Protocol EN3835-303
Site #1349
4425 Conlin Street
Metairie, LA 70006
Inspection Dates: 2-6 December 2019

At this site for Protocol EN3835-303, 26 subjects were screened, 23 were enrolled, 22 completed the study, and 1 subject withdrew early. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, source data and records, eCRFs, eCOA primary efficacy endpoint data (i.e., PR-PCSS and CR-PCSS), drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for 9 of the 23 subjects who were enrolled was conducted.

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint data were reviewed and verified against the data listings provided by the sponsor for 9 of the 23 subjects enrolled; no discrepancies were noted.

4. Michael Gold, M.D.
Protocol EN3835-303
Site #1299
2000 Richard Jones Road, Suite 223
Nashville, TN 37215
Inspection Dates: 6-9 January 2020

At this site for Protocol EN3835-303, 49 subjects were screened, 37 were enrolled, 36 completed the study, and 1 subject withdrew due to an adverse event (Subject (b) (6); randomized to EN3835 1.68 mg/left buttock; pain, bruising, knots in left buttock). Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, source data and records, eCRFs, eCOA primary efficacy endpoint data (i.e., PR-PCSS and CR-PCSS), drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all 37 subjects who were enrolled was conducted.

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint data were reviewed and verified against the data listings provided by the sponsor for all 37 subjects who were enrolled. Three minor data discrepancies were noted for Subject # (b) (6) (EN3835 1.68 mg/Right buttock) for the Day 71 values entered for PR-PCSS, Investigator Global Aesthetic Improvement Scale, and Subject Satisfaction with

Cellulite Treatment Assessment.

Reviewer's comments: The FDA field investigator further explored the root cause of the Day 71 data discrepancies for Subject # (b) (6) with the sponsor. The sponsor stated that per their Statistical Analysis Plan (SAP), missing Day 71/early termination values would have baseline values carried forward for analysis. However, the sponsor inadvertently pulled the baseline values forward for Day 71 for all subjects who early terminated when they prepared the BIMO data listings submitted to FDA. The BIMO data listings should have reflected the actual Day 71/early termination values for the PR-PCSS, Investigator Global Aesthetic Improvement Scale, and Subject Satisfaction with Cellulite Treatment Assessment that were entered in the study database.

In an email communication, dated 1 April 2020, with FDA's Office of Biostatistics (OB) and the Office of Scientific Investigations, OB confirmed that this handling of missing data was pre-specified in their SAP, and all subjects with missing data were correctly imputed as non-responders.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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Central Doc. Rm. BLA 761146
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DNP/Medical Officer/ Melinda McCord
DNP/Clinical Team Leader/ Gordana Diglisic
DNP/Division Director/ Kendall Marcus
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: March 30, 2020 **Date Consulted:** November 4, 2019

From: Jane Liedtka M.D., Medical Officer (MO), Maternal Health
Division of Pediatric and Maternal Health (DPMH)

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

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Melinda McCord, M.D., MO
Division of Dermatology and Dental (DDD)

Drug: collagenase clostridium histolyticum (CCH) for injection, for subcutaneous use

BLA: 761146

Indication: CCH is a combination of bacterial collagenases indicated for the treatment of moderate to severe cellulite in the buttocks of adult women.

Applicant: Endo Global Aesthetics Limited

Subject: Pregnancy and Lactation Labeling Rule (PLLR) language (Original BLA)

Materials Reviewed:

- Applicant's background package for BLA 761146 submitted on 9/6/19.

Consult Question: Please review the labeling, pregnancy data from the development program, provide recommendations on section 8 USE IN SPECIFIC POPULATIONS of labeling.

INTRODUCTION AND BACKGROUND

On November 4, 2019, DDD consulted DPMH to provide input regarding the appropriate format and content of Section 8 of collagenase clostridium histolyticum (CCH) for injection, for subcutaneous use, BLA 761146 labeling for compliance with the PLLR format.

- CCH is a parenteral lyophilized product comprised of two collagenase enzymes in an approximate 1:1 mass ratio: Collagenase I (AUX-I, Clostridial type I collagenase) and Collagenase II (AUX-II; Clostridial type II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. CCH for injection for the indication of cellulite is not quantifiably absorbed following injection, and maternal use is not expected to result in fetal exposure to the drug.
- Endo Global Aesthetics Limited (EGAL) is proposing the use of subcutaneous CCH for the treatment of adult females with moderate to severe edematous fibrosclerotic panniculopathy (EFP), otherwise known as cellulite.
- XIAFLEX® contains the same active ingredient as CCH (with minor formulation differences (b) (4) (b) (4) and was developed by Auxilium Pharmaceuticals, Inc¹. XIAFLEX was approved in the US on February 2, 2010 for
 - adult patients with Dupuytren's contracture (DC) with a palpable cord
 - adult men with Peyronie's disease (PD) with a palpable plaque and curvature deformity of at least 30 degrees. This indication was approved on December 6, 2013.

Table 1: Collagenase Clostridium Histolyticum Drug Characteristics²

Drug Class	Bacterial collagenase
Mechanism of action	Proteinase that hydrolyzes collagen in its native helical conformation under physiological conditions. The exact mechanism of action is unknown.
Molecular weight	Collagenase AUX-I: 114 kilodaltons; Collagenase AUX-II: 113 kilodaltons
Pharmacokinetics	Pharmacokinetics of collagenases clostridium histolyticum were evaluated in 140 female subjects with cellulite in four clinical studies. Plasma concentrations of AUX-I and AUX-II were below the low limit of quantitation of 5 ng/mL and 25 ng/mL, respectively, in all subjects that received a single dose of collagenases clostridium histolyticum up to 3.36 mg in up to 4 treatment areas (up to 0.84 mg per treatment area).
Immunogenicity	In 4 placebo controlled clinical trials for cellulite, 535 subjects received treatment in the buttock and 118 subjects received treatment in the thigh, 53% of subjects had antibodies against AUX-I detected and 24% of subjects had antibodies against AUX-II detected after the first injection of CCH. After the second treatment visit, greater than 96% CCH-treated subjects developed antibodies to AUX-I and/or AUX-II. There were no serious hypersensitivity reactions that were reported.

¹ EGAL acquired Auxilium on 1/29/15, EGAL was authorized to communicate with FDA on all matters on Auxilium's behalf. The ownership of CCH was transferred from Auxilium to EGAL on 6/28/19.

²Reviewer's table

Reviewer's Comment

Although there was no quantifiable systemic absorption of AUX-I and AUX-II, clinical trials have demonstrated the presence of antibodies against AUX-I and AUX-II, which suggests that there may be minimal systemic absorption that is occurring.

Current State of the Labeling³

- The most recently revised labeling for Xiaflex is in Physician Labeling Rule (PLR) format but within subsection 8.1 the labeling is in the PLLR hybrid format; ie retains the pregnancy category B designation but has a risk summary.
- There is a boxed warning for “Corporal rupture (penile fracture)” and a statement that Xiaflex is only available through a Risk Evaluation and Mitigation Strategy (REMS).
- There are contraindications for Peyronie’s plaques that involve the penile urethra and for a history of hypersensitivity to XIAFLEX or to collagenase used in other therapeutic applications in the label.
- Warnings and Precautions include
 - Tendon rupture or serious injury to the injected finger/hand: Avoid injecting XIAFLEX into tendons, nerves, blood vessels, or other collagen-containing structure of the hand. Injection into these structures may result in possible permanent injury, such as tendon rupture, ligament damage, or skin laceration.
 - Corporal rupture (penile fracture) or other serious injury to the penis: Avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis. Injection into these structures may result in possible permanent injury such as corporal rupture (penile fracture).
 - Hypersensitivity reactions, including anaphylaxis: Healthcare providers should be prepared to address hypersensitivity reactions, including anaphylaxis, following XIAFLEX injections.
 - Patients with abnormal coagulation: Use with caution, including in patients who have received anticoagulant medications other than low-dose aspirin within 7 days of the injection.
- Under subsection 8.1, Pregnancy, the labeling categorizes the product as “Pregnancy Category B” and goes on to state
There are no adequate and well-controlled studies of XIAFLEX in pregnant women. Because animal reproduction studies are not always predictive of human response, XIAFLEX should be used during pregnancy only if clearly needed.

Risk Summary

Based on animal data, XIAFLEX is not predicted to increase the risk for major developmental abnormalities in humans.

Human Data

Human pharmacokinetic studies showed that XIAFLEX levels were not quantifiable in the systemic circulation following injection into a Dupuytren’s cord. Low levels of XIAFLEX were quantifiable in the plasma of evaluable male subjects for up to 30

³ Xiaflex label approved in June 2018.

minutes following administration of XIAFLEX into the penile plaque of subjects with Peyronie's disease [see *Clinical Pharmacology* (12.3)].

Almost all patients develop anti-product antibodies (anti-AUX-I and anti-AUX-II) after treatment with XIAFLEX, and the clinical significance of anti-product antibody formation on a developing fetus is not known [see *Adverse Reactions* (6)].

Animal Data

Reproduction studies have been performed in rats with intravenous exposures up to approximately 11 times the maximum recommended human dose (MRHD) of XIAFLEX on a mg/m^2 basis and have revealed no evidence of impaired fertility or harm to the fetus due to CCH.

- Under subsection 8.3, Nursing Mothers, the labeling states
It is not known whether collagenase clostridium histolyticum is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XIAFLEX is administered to a nursing woman.
- Under subsection 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, the labeling states
 - Carcinogenesis
Long-term animal studies to evaluate the carcinogenic potential of collagenase clostridium histolyticum have not been conducted.
 - Mutagenesis
Purified collagenase clostridium histolyticum was not mutagenic in Salmonella typhimurium (AMES test) and was not clastogenic in both an in vivo mouse micronucleus assay and an in vitro chromosomal aberration assay in human lymphocytes.
 - Impairment of Fertility
Collagenase clostridium histolyticum did not impair fertility and early embryonic development when administered intravenously in rats at exposures up to approximately 11 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.

REVIEW

Pregnancy

Nonclinical Experience

In animal reproduction studies, intravenous administration of collagenase clostridium histolyticum to pregnant rats during organogenesis at doses up to 0.13 mg/rat revealed no evidence of harm to the fetus.

For further details, the reader is directed to the Nonclinical Review by Jill Merrill, PhD.

Applicant's Review of Literature

The sponsor was not asked to perform a literature search since there is no quantifiable systemic absorption with local injection into the buttocks for treatment of cellulite.

Review of Pharmacovigilance Database (PVDB)

A review was performed of the sponsor's PVDB, including the development program for the original indications of Dupuytren's contracture (DC) and Peyronie's disease (PD). The following pregnancies were reported during the development program for cellulite:

- Subject (b) (6) was reported to have become pregnant after Study -201 in which she received 3 treatment sessions of CCH 0.84 mg. Her pregnancy was reported to the site on (b) (6), 1 month after her last treatment on (b) (6). The pregnancy was lost/spontaneously aborted on (b) (6) at approximately 6 to 7 weeks. The subject informed the site that the pregnancy was not expected to continue as she had a history of spontaneous abortions.
- Subject (b) (6) was reported to have become pregnant after Study -202 study in which she received 3 treatment sessions of CCH 0.84 mg. Her pregnancy was reported 8 months after her last treatment. No additional information regarding the pregnancy was reported.
- Subject (b) (6) became pregnant during Study -205 while using condoms and spermicide after receiving 2 treatment sessions of CCH 1.68 mg. The subject had a normal pregnancy and delivered a healthy term infant. At 2 months of age, the child was developing normally.

One additional report of pregnancy was received for a female subject enrolled in a clinical study for the treatment of adhesive capsulitis of the shoulder and received CCH. The pregnancy outcome is unknown. There were also 3 reports of pregnancies occurring in women whose male partner received CCH in a clinical study for the treatment of PD. The pregnancy outcome is unknown in 1 case and normal births were reported in the 2 other cases. There were no reports of pregnancies in subjects treated with CCH for DC.

DPMH's Review of the Literature

DPMH conducted a search of published literature in PubMed using the search terms "CCH and pregnancy" "CCH and pregnant women," "CCH and pregnancy and birth defects," "CCH and pregnancy and congenital malformations," "CCH and pregnancy and stillbirth," "CCH and spontaneous abortion" and "CCH and pregnancy and miscarriage" covering up through February 19, 2020. No relevant publications were identified.

CCH is referenced in Briggs⁴ *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. The author's give a pregnancy recommendation: No Human Data—Probably Compatible and goes on to state

After injection into a Dupuytren's cord, neither of the collagenases had quantifiable levels in the systemic circulation (the lower limit of quantification for AUX I and AUX II in human plasma is 5 and 25 ng/mL, respectively)...It

⁴ Briggs, GG, Freeman, RK, & Yaffe, SJ. (2015). *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

is not known if the two collagenases cross the human placenta. The molecular weights of collagenase AUX-1 and collagenase AUX-II are 114,000 and 113,000, respectively, and nonquantifiable systemic levels suggest that clinically significant exposure of the embryo or fetus is unlikely.

Micromedex⁵ notes that CCH is a “Pregnancy Category B” drug, that it is “unknown if it crosses the placenta”, and that “Infant risk cannot be ruled out”.

TERIS⁵ notes “Magnitude of Teratogenic Risk to Child Born After Exposure During Gestation is undetermined. The Quality and Quantity of Data on Which Risk Estimate is Based is none. A small risk cannot be excluded, but a high risk of congenital anomalies in the children of women treated with CCH during pregnancy is unlikely.

Lactation

Nonclinical Experience

There are no animal studies of CCH use during lactation.

Applicant’s Review of Literature

The sponsor was not asked to perform a literature search since there is no systemic absorption with local injection into the buttocks for treatment of cellulite.

DPMH’s Review of Literature

DPMH conducted a search of published literature in PubMed through February 19, 2020 using the search terms “CCH and lactation” and “CCH and breastfeeding” and found no publications.

CCH is referenced in Briggs³ *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. The author’s give a breastfeeding recommendation: No Human Data—Probably Compatible, and go on to state

No reports on the use of collagenase C. histolyticum during lactation have been located. The molecular weights of collagenase AUX-1 and collagenase AUX-II are 114,000 and 113,000, respectively, and, combined with the nonquantifiable systemic levels, suggest that the presence in milk of clinically significant amounts is unlikely.

CCH is not referenced in Hale’s *Medications and Mother’s Milk*⁶ or in LactMed.⁷

⁵ (b) (4) information, <http://www.micromedexsolutions.com/>. Accessed 2/19/20.

⁶ Hale, Thomas (2017) *Medications and Mothers’ Milk*. Amarillo, Texas Hale Publishing.

⁷ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed August 30, 2019.

Review of Pharmacovigilance Database

According to the Applicant, no cases of exposure to CCH via breast milk were reported in the PVDB.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

To evaluate both the potential effects of CCH or antibodies generated in response to repeated injection, an intravenous fertility and general reproduction toxicity study (Study DLB00012) and an intravenous developmental toxicity study (Study DLB00009) were performed in rats as part of the development program for XIAFLEX (BLA 125,338). Neither study showed any effects on reproduction or embryo-fetal up to the highest dose levels tested which were approximately 43 times the human dose of 0.84 mg on a mg/kg basis.

For further details, the reader is directed to the Nonclinical Review by Jill Merrill, PhD.

Applicant's Review of Literature

The sponsor was not asked to perform a literature search since there is no systemic absorption with local injection into the buttocks for treatment of cellulite.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed through February 19, 2020 regarding the use of CCH and its effects on fertility and found no new relevant publications.

DISCUSSION AND CONCLUSIONS

Pregnancy

Due to the lack of systemic exposure noted in the clinical pharmacokinetic study, maternal use of CCH is not expected to result in fetal exposure to the drug. CCH is not absorbed systemically following injection into the buttocks. See DPMH proposed labeling below for further details.

Lactation

CCH is not quantifiably absorbed by the mother following injection into the buttocks, therefore, breastfeeding is not expected to result in the exposure of the child to CCH [see *Clinical Pharmacology (12.3)*]. There are no data on the presence of CCH in human milk, effects of CCH on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CCH and any potential adverse effects on the breastfed child from CCH, or from the underlying maternal condition.

In addition, since CCH is not quantifiably absorbed, a clinical lactation study is not required.

Females and Males of Reproductive Potential

There are no concerns leading to a need for pregnancy testing or contraception. No evidence of fertility effects was seen in animals. Therefore, DPMH recommends omitting subsection 8.3 from labeling for CCH.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of CCH labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DDD on 3/30/2020. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Collagenase Clostridium Histolyticum (CCH) for Injection Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Collagenase clostridium histolyticum (CCH) injection is not quantifiably absorbed following injection, and maternal use is not expected to result in fetal exposure to the drug [*see Clinical Pharmacology (12.3)*]. There are no available data on collagenase clostridium histolyticum use in pregnant women to evaluate for a drug- associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, intravenous administration of collagenase clostridium histolyticum to pregnant rats during organogenesis at doses up to 0.13 mg/rat revealed no evidence of harm to the fetus (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

CCH is not quantifiably absorbed by the mother following injection; therefore, breastfeeding is not expected to result in the exposure of the child to CCH [*see Clinical Pharmacology (12.3)*]. There are no data on the presence of CCH in human milk, the effects of CCH on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CCH and any potential adverse effects on the breastfed child from CCH, or from the underlying maternal condition.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANE E LIEDTKA
03/30/2020 04:01:15 PM

MIRIAM C DINATALE
03/30/2020 04:04:56 PM

LYNNE P YAO
04/01/2020 03:23:56 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	March 18, 2020
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761146
Product Name, Dosage Form, and Strength:	(collagenase clostridium histolyticum-xxxx) ^a for injection, 0.92 mg/vial and 1.84 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Endo Global Aesthetics Limited
FDA Received Date:	February 12, 2020
OSE RCM #:	2019-1865
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

^a The proposed nonproprietary name has not yet been conditionally accepted. We therefore refer to the proposed product as “collagenase clostridium histolyticum-xxxx” throughout this review in place of the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for collagenase clostridium histolyticum-xxxx for injection, the Division of Dermatology and Dental Products (DDDP) requested that we review the proposed labels and labeling for areas 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 Label and Labeling 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), Patient Package Insert (PPI), container labels and carton labeling for collagenase clostridium histolyticum-xxxx for injection. We noted that the label and labeling can be improved to prevent wrong drug and wrong dose errors, to facilitate product identification, and to prevent deteriorated drug errors. The carton labeling can also be improved to align formatting of product identifiers with the FDA released draft guidance on product identifiers^b. We note the use of the proposed proprietary name, (b) (4) *** which we found unacceptable due to orthographic and phonetic similarities and shared product characteristics with other marketed products^c.

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

^c Vaughan, V. Proprietary Name Review for (b) (4) *** (BLA 761146). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 05. Panorama No. 2019-36562853.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved. We provide 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 DENTAL PRODUCTS (DDDP)

A. General Comments

1. We recommend the placeholder, “<PRODUCT NAME>” be removed throughout the labels and labeling once a new name is found conditionally acceptable.
2. We (b) (4) defer to the Office of Pharmaceutical Quality (OPQ) to determine if it is appropriate to use the package type term, “single-dose” (b) (4) throughout the labeling. We recommend that the carton labeling be updated to match the correct package type term for consistency.

4.2 RECOMMENDATIONS FOR ENDO GLOBAL AESTHETICS LIMITED

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

A. General Comments (Container labels & Carton Labeling)

1. The proposed proprietary name, (b) (4) used throughout the container label and carton labeling, was found unacceptable by DMEPA^d. Remove the proposed proprietary name, (b) (4) throughout the PI and PPI. Until a name is found to be conditionally acceptable, the placeholder, “TRADENAME” may be used. Once a proprietary name is found conditionally acceptable, the placeholder “TRADENAME” must be replaced with the proprietary name on the container labels and carton labeling and the revised labels and labeling must be submitted to the Agency for review.
2. Revise the presentation of the names on the container labels and carton labeling as follows in accordance with *21 CFR 610.62(a)* and Draft Guidance: Safety Considerations for Container Labels:

collagenase clostridium histolyticum-xxxx

TRADENAME

X.XX mg per vial

^d Bui Nguyen, T. Proprietary Name Request Unacceptable: (b) (4) *** for BLA 761146. Silver Spring (MD): FDA, CDER, OSE (US) 2020 MAR 09.

for Injection

for subcutaneous use

3. We note the National Drug Code (NDC) number for the vials of collagenase clostridium histolyticum is the same as the NDC on corresponding vial of the diluent. The NDCs on vials of the diluent should have different product codes (middle segment) than the NDCs on the vials of collagenase clostridium histolyticum because the diluent is not the same product as the vial containing the collagenase clostridium histolyticum. Additionally, the NDCs on the cartons need different product codes than those the corresponding vial of diluent and collagenase clostridium histolyticum. Please revise the NDCs accordingly.
4. Decrease the prominence of the statement “Rx Only” as this information appears more prominent than the established name on the principal display panel.

B. Container Labels

1. We did not identify a placeholder (“LOT” or “EXP”) for the lot number and expiration date on the proposed container labeling. Ensure that the lot number and expiration date are presented in accordance with 21 CFR 201.10(i) and 21 CFR 201.137, and that they are clearly differentiated from one another.^e Ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.^f

C. Carton Labeling

1. Add the net quantity to the Principal Display Panel (PDP), as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013. For example:

This carton contains:

- 1 TRADENAME single-dose vial , X.XX mg
- 1 Diluent for TRADENAME single-dose vial, XX mL

Ensure the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

^e Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

^f Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

2. To prevent partial dispensing, add the following statement: “Dispense entire carton”.
3. To facilitate quicker identification of the product, we recommend that the middle digits of the NDC be different, not similar (i.e. middle digits differ only by one digit) or increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number and/or put them in bold type. For example: XXXXX-**XXX**-XX.
4. Revise the storage section to add a bolded statement to read as follows: “Must be refrigerated, store at 2°C to 8°C (36°F to 46°F)”. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked. If space permits, information on the post-reconstitution expiration date and post-reconstitution storage should also be included as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
5. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read “prescribing information.”
6. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.⁹ 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]

We recommend that you review the draft guidance for the recommended format.

⁹ 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 collagenase clostridium histolyticum-xxxx received on September 6, 2019 from Endo Global Aesthetics Limited, and Xiaflex).

Table 2. Relevant Product Information for collagenase clostridium histolyticum-xxxx and Xiaflex		
Product Name	collagenase clostridium histolyticum-xxxx	Xiaflex ^h
Initial Approval Date	N/A	February 2, 2010
Nonproprietary Name	collagenase clostridium histolyticum-xxxx	collagenase clostridium histolyticum
Indication	treatment of moderate to severe cellulite in the buttocks of adult women	- treatment of adult patients with Dupuytren's contracture with a palpable cord - treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy
Route of Administration	subcutaneous	intralesional
Dosage Form	for injection	for injection
Strength	0.92 mg/vial and 1.84 mg/vial	0.9 mg/vial
Dose and Frequency	Inject 0.84 mg per treatment area as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection). A treatment area is defined as a single buttock receiving up to 12 injections, 0.3 mL each (up to a total of 3.6 mL). A treatment visit may consist of up to 2 treatment areas. Treatment visits should be repeated every 21 days for 3 treatment visits.	Dupuytren's contracture- The dose of XIAFLEX is 0.58 mg per injection into a palpable cord with a contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint. Four weeks after the XIAFLEX injection and finger extension procedure, if a MP or PIP contracture remains, the cord may be re-injected with a single dose of 0.58 mg of XIAFLEX and the finger extension procedure may be repeated (approximately 24 to 72 hours after injection). Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.

^h Xiaflex [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 MAR 02. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=805cecd0-fd1f-11dd-87af-0800200c9a66>.

		Perform up to two injections in the same hand according to the injection procedure during a treatment visit. Two palpable cords affecting two joints may be injected or one palpable cord affecting two joints in the same finger may be injected at two locations during a treatment visit. If patient has other palpable cords with contractures of MP or PIP joints, these cords may be injected with XIAFLEX at other treatment visits approximately 4 weeks apart. • Peyronie's disease - The dose of XIAFLEX is 0.58 mg per injection administered into a Peyronie's plaque. If more than one plaque is present, inject into the plaque causing the curvature deformity. A treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consists of two XIAFLEX injection procedures and one penile modeling procedure. The second XIAFLEX injection procedure is performed 1 to 3 days after the first. The penile modeling procedure is performed 1 to 3 days after the second injection of the treatment cycle. The interval between treatment cycles is approximately six weeks. The treatment course therefore, consists of a maximum of 8 injection procedures and 4 modeling procedures. If the curvature deformity is less than 15 degrees after the first, second or third treatment cycle, or if the healthcare provider determines that further treatment is not clinically indicated, then the subsequent treatment cycles should not be administered
How Supplied	(b) (4) glass vials containing 0.92 mg or 1.84 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder.	Single-use, glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder. Sterile diluent for reconstitution is available in single-use, glass vials containing 3 mL of 0.3

	Sterile diluent for reconstitution is available in (b) (4), glass vials containing 4 mL or 8 mL of 0.03% calcium chloride dihydrate in 0.6% sodium chloride. <table><tr><th>NDC Number</th><th>Package Size</th></tr><tr><td>73611-(b) (4)05</td><td>Single treatment area: (b) (4)</td></tr><tr><td>73611-(b) (4)10</td><td>Two treatment areas: (b) (4)</td></tr></table>	NDC Number	Package Size	73611-(b) (4)05	Single treatment area: (b) (4)	73611-(b) (4)10	Two treatment areas: (b) (4)	mg/mL calcium chloride dihydrate in 0.9% sodium chloride. <table><tr><th>NDC Number</th><th>Package Size</th></tr><tr><td>66887-003-01</td><td>Single-use package: 1 carton containing a single-use vial of XIAFLEX and a single-use vial of sterile diluent</td></tr><tr><td>66887-003-02</td><td>Dual-Pack (two single-use packages): 1 box containing 2 cartons, each containing a single-use vial of XIAFLEX and a single-use vial of sterile diluent</td></tr></table>	NDC Number	Package Size	66887-003-01	Single-use package: 1 carton containing a single-use vial of XIAFLEX and a single-use vial of sterile diluent	66887-003-02	Dual-Pack (two single-use packages): 1 box containing 2 cartons, each containing a single-use vial of XIAFLEX and a single-use vial of sterile diluent
NDC Number	Package Size													
73611-(b) (4)05	Single treatment area: (b) (4)													
73611-(b) (4)10	Two treatment areas: (b) (4)													
NDC Number	Package Size													
66887-003-01	Single-use package: 1 carton containing a single-use vial of XIAFLEX and a single-use vial of sterile diluent													
66887-003-02	Dual-Pack (two single-use packages): 1 box containing 2 cartons, each containing a single-use vial of XIAFLEX and a single-use vial of sterile diluent													
Storage	Prior to reconstitution, the vials of collagenase clostridium histolyticum and diluent should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. The reconstituted collagenase clostridium histolyticum solution can be kept at room temperate (20°C to 25°C/68°F to 77°F) for up to 8 hours or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 72 hours prior to administration.	Prior to reconstitution, the vials of XIAFLEX and diluent should be stored in a refrigerator at 2° to 8°C (36° to 46°F). Do not freeze. The reconstituted XIAFLEX solution can be kept at room temperature (20° to 25°C/68° to 77°F) for up to one hour or refrigerated at 2° to 8°C (36° to 46°F) for up to 4 hours prior to administration												
Container Closure	N/A	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,ⁱ along with postmarket medication error data, we reviewed the following collagenase clostridium histolyticum-xxxx labels and labeling submitted by Endo Global Aesthetics Limited.

- Container labels received on February 12, 2020
- Carton labeling received on February 12, 2020
- Patient Package Insert (Image not shown) received on February 12, 2020, available from <\\cdsesub1\evsprod\bla761146\0014\m1\us\draft-labeling-text-patient-information.pdf>
- Prescribing Information (Image not shown) received on February 12, 2020, available from <\\cdsesub1\evsprod\bla761146\0014\m1\us\draft-labeling-text-pi.pdf>

G.2 Label and Labeling Images

Container Labels



3 Pages of Draft Labeling have been Withheld in Full as
B4(CCI/TS) Immediately Following this Page

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
03/18/2020 03:11:31 PM

SEVAN H KOLEJIAN
03/18/2020 04:24:40 PM