CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761192Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	December 28, 2022
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761192
Product Name and Strength:	Nexobrid (anacaulase-bcdb) for topical gel, 8.8%
Applicant/Sponsor Name:	MediWound, Ltd
OSE RCM #:	2022-589-1
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 20, 2022 for Nexobrid. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Nexobrid (Appendix A) to determine if it is 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

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

[a] Patel, M. Label and Labeling Review for Nexobrid (BLA 761192). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 08. RCM No.: 2022-589.

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/s/

MADHURI R PATEL
12/28/2022 10:00:48 PM

MISHALE P MISTRY
12/29/2022 10:36:29 AM

Memo To File

Date	December 15, 2022
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jennifer Harmon, Pharm.D., RPM Brenda Carr, MD, Medical Reviewer Kevin Clark, MD, Medical Team Leader Shari Targum, MD, Division Director Division of Dermatology and Dentistry (DDD)
BLA #	761192
Applicant	MediWound, Ltd
Drug	NexoBrid (concentrate of proteolytic enzymes enriched in Bromelain)
NME	Yes
Proposed Indication	For eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.
PDUFA Date	December 29, 2022

The following significant issues were related to the conduct of Protocol MW2010-03-02 (the DETECT Study) and were communicated to the applicant in the June 25, 2021 Complete Response Letter. These issues were observed during routine PDUFA and for-cause good clinical practice (GCP) inspections and had an impact on the (b) (4)

(b) (4)

FDA recommended that the applicant perform quality control audits of investigator sites participating in the DETECT study (b) (4)

(b) (4)

OSI recommends that sensitivity analyses be performed to further assess the impact of the (b) (4)

{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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DDD/Clinical Reviewer/Brenda Carr
DDD/Project Manager/Jennifer Harmon
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/ Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Acting Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cheryl Grandinetti
OSI/GCPAB Program Analyst/Yolanda Patague

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 8, 2022

Date of Consult Request: October 21, 2022

From: CAPT Anissa Davis-Williams, RN, MSN, MPH, Senior Regulatory Health Project Manager, Division of Pediatrics and Maternal Health (DPMH)

To: Jennifer Harmon, Regulatory Health Project Manager, Division of Dermatology and Dental (DDD)

BLA Number: 761192

Drug: Concentrate of proteolytic enzymes enriched in bromelain

Applicant: MediWound, Ltd
Indication: For eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.

DDD submitted a consult to DPMH dated October 21, 2022, requesting our assistance with reviewing the labeling submitted with the Applicant's resubmission of their application after a Complete Response, which was issued June 25, 2021.

DPMH reviewed labeling during the first review cycle and completed a written review, on February 19, 2021. For this resubmission, DPMH attended an internal labeling meeting on October 19, 2022, and did not have any significant changes to their prior proposed labeling review.

Therefore, this memorandum will close out the consult request.

DPMH RPM- CAPT Anissa Davis-Williams, RN, B.S.N., M.P.H.
DPMH- Supervisory Consumer Safety Officer- George Greeley, M.S., M.B.A.
DPMH Pediatrics MO Reviewer- Carrie Ceresa, M.D.
DPMH Pediatrics Team Leader- Miriam Dinatale, M.D.
DPMH Director- Lynne Yao, M.D., M.P.H.

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/s/

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LABEL AND LABELING REVIEW

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

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	December 8, 2022
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761192
Product Name, Dosage Form, and Strength:	Nexobrid (anacaulase-bcdb) for topical gel, 8.8%[a]
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	MediWound, Ltd
FDA Received Date:	July 1, 2022
TTT ID #:	2022-589
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

[a] We note the Applicant submitted the strengths as 2 g and 5 g for this product. However, the Office of Pharmaceutical Quality (OPQ) has determined the strength as 8.8%.

1 REASON FOR REVIEW

As part of the approval process for Nexobrid (anacaulase-bcdb) for topical gel, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Nexobrid Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

We previously reviewed proposed Prescribing Information (PI), container labels, and carton labeling for Nexobrid under the initial BLA submission.[b] However, on June 25, 2021, a Complete Response action was issued for BLA 761192, and the recommendations were not sent to the Applicant. The Applicant submitted revised Prescribing Information (PI), container labels, and carton labeling as part of the resubmission on July 1, 2022.

3 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), container labels, and carton labeling. We note the PI can be improved to place adequate space between the numerical dose and vial size and

[b] Patel, M. Label and Labeling Review for Nexobrid (BLA 761192). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 23. RCM No.: 2020-1350.

unit of measure [redacted] (b) (4) We also note reference to [redacted] (b) (4) [redacted] (b) (4) which will be removed, per discussion with the Clinical team, as all necessary information needed for the preparation and administration of the product is contained in the PI. We also note that the Office of Pharmaceutical Quality (OPQ) has determined the strength as 8.8% and the Office of Biotechnology Products (OBP) will recommend the Applicant update the strength presentation accordingly. Additionally, we find the container labels and carton labeling can be improved to prevent wrong drug/dose errors, deteriorated drug errors, and wrong technique errors.

5 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling for NexoBrid can be improved. We recommend the following be implemented prior to approval of this BLA.

5.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. General Comment

1. We recommend updating the nonproprietary name to 'anacaulase-bcdb' throughout the labeling.

B. Prescribing Information

1. How Supplied/Storage and Handling

a. To improve readability, place adequate space between the numerical dose and unit of measure ([redacted] (b) (4)).

5.2 RECOMMENDATIONS FOR MEDIWOUND, LTD

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

A. General Comments (Container labels & Carton Labeling)

1. Revise the nonproprietary name, anacaulase-bcdb, to the labels and labeling and submit for our review.
2. To improve readability, place adequate space between the numerical dose and unit of measure (e.g. 2 g instead of 2g).
3. As currently presented for the professional sample container labels and carton labeling, the National Drug Code (NDC) is denoted by a placeholder (NDC 69866-XXXX-X). Replace these NDC placeholders with the actual NDC when it is determined and submit the revised labels and labeling to the Agency for review.
4. Revise and bold the statement as follows: "Store and transport Nexobrid upright and refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. DO NOT FREEZE.". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

B. Container Labels

1. For the container labels of the gel vehicle, increase the prominence of the words "Gel" so that it is the most prominent word on the label similar to:

   Gel vehicle

   For use with anacaulase-bcdb lyophilized powder for topical gel

   We recommend this to minimize the risk of wrong drug errors where the gel vehicle is administered without the drug. Additionally, add the statement *"For drug preparation use only – mix powder and gel prior to application as directed"* to the bottom of the PDP (space permitting) or on the side panel.

2. Reorient the linear barcodes to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial/jar curvature.[c]

[c] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nexobrid received on July 1, 2023 from MediWound, Ltd.

Table 2. Relevant Product Information for Nexobrid	
Initial Approval Date	N/A
Nonproprietary Name	anacaulase-bcdb
Indication	eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.
Route of Administration	topical
Dosage Form	for topical gel
Strength	8.8%
Dose and Frequency	• 2 g lyophilized powder mixed with 20 g gel per 1% total body surface area (TBSA) of an adult, or • 5 g lyophilized powder mixed with 50 g gel per 2.5% TBSA of an adult. • The powder and gel are mixed to produce NexoBrid (b) (4) (b) (4) (b) (4) NexoBrid may be applied to an area of up to 15% TBSA in one application. A second application of NexoBrid may be applied twenty-four (24) hours later to the same or new burn wound area. The total treated area for both applications must not exceed 20% TBSA.
How Supplied	• NexoBrid is provided as two components that are mixed prior to application. • Each package of NexoBrid includes: one single use vial of powder, sealed with a rubber stopper and covered with a flip cap; and one jar of gel sealed with a rubber stopper and covered with a screw cap. • NexoBrid carton, NDC 69866-2002-3, contains o 2g sterile lyophilized powder and 20g sterile gel • NexoBrid carton, NDC 69866-2005-3, contains o 5g sterile lyophilized powder and 50g sterile gel

Storage	• Store and transport refrigerated (2 to 8°C). • Store upright. • Protect from light. • DO NOT FREEZE.
Container Closure	one single use 50 mL glass vial of powder, sealed with a rubber stopper and covered with a flip cap; and one single use 150 mL glass jar of gel sealed with a rubber stopper and covered with a screw cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 11, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'nexobrid'. Our search identified one previous review[d], and we considered our previous recommendations to see if they are applicable for this current review.

[d] Patel, M. Label and Labeling Review for Nexobrid (BLA 761192). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 23. RCM No.: 2020-1350.

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,[e] along with postmarket medication error data, we reviewed the following Nexobrid labels and labeling submitted by MediWound, Ltd.

- Container Labels received on July 1, 2022
- Carton Labeling received on July 1, 2022
- Professional Sample Container Labels received on July 1, 2022
- Professional Sample Carton Labeling received on July 1, 2022
- Prescribing Information (Image not shown) received on July 1, 2022, available from \\CDSESUB1\EVSPROD\bla761192\0036\m1\us\114-labeling\draft\labeling\draft-labeling-text-word.docx

G.2 Label and Labeling Images

Container Labels

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

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/s/

MADHURI R PATEL
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	BLA-761192
Submission Number	001
Submission Date	6/29/2020
Date Consult Received	8/12/2020
Drug Name	NexoBrid (concentrate of proteolytic enzymes enriched in bromelain)
Indication	Eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns
Therapeutic dose	2 grams of NexoBrid sterile lyophilized powder mixed with 20 grams of sterile gel vehicle per 1% total body surface area (TBSA) or 5 grams of NexoBrid sterile lyophilized powder mixed with 50 grams of sterile gel vehicle per 2.5% TBSA to achieve a final concentration of (b) (4) grams/gram (1:10 ratio).
Clinical Division	DDDP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 8/12/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-065448 dated 10/16/2012 in DARRTS (link);
- Previous IRT review under IND-065448 dated 11/16/2018 in DARRTS (link);
- Investigator's brochure Ed.18 under IND65448 (Appendix, SN0142; link);
- Sponsor's clinical study protocol # MW2010-03-02 (SN0001; link);
- Sponsor's clinical study report # MW2010-03-02 (SN0001; link);
- Sponsor's cardiac safety assessment report # MW2010-03-02 (SN0001; link);
- Sponsor's proposed product label (SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (IND65448, SN0064; link).

1 SUMMARY

No large (>20 msec) mean increases in the QTc interval was detected when NexoBrid was applied to a mean of 6% total body surface in this QT assessment. We are reluctant to draw conclusions of lack of an effect in an absence of a positive control or large exposure margin, or an integrated nonclinical safety assessment conduct according to best practices (ICH S7b Q&A 1.1 and 1.2).

The clinical effect of NexoBrid was evaluated in a multicenter, multinational, randomized, controlled, assessor blinded study performed in patients with thermal burns (Study #

MW2010-03-02). The study evaluated safety and efficacy of NexoBrid compared to the gel vehicle and the standard of care (SOC - surgical and/or nonsurgical procedures). In this sub-study, NexoBrid was compared to the gel vehicle only (placebo). The study utilized therapeutic dose; however, the actual doses utilized included ~42% of targeted theoretical TBSA (6% *vs*. 15%).

The data were analyzed using by timepoint analysis, and at the therapeutic dose studied, did not suggest that NexoBrid is associated with large mean increases in the QTc interval – see Table 1 for overall results.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time	ΔΔQTcF	90% CI
QTc	Topical NexoBrid Gel	4 h	7.5 msec	(0.2, 14.9)

For further details on the FDA analysis, please see section 4.

The results from this analysis are supported by the available categorical analysis (Section 4.4) and exposure-response analysis (Section 4.5).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the Section 12.2 (SN0001; link). Below are proposed edits from the IRT (*addition*). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

Reviewer's Comments: In Section 2 (Dosage and Administration) the sponsor describes that 'NexoBrid can be applied to an area of up to 15 % total body surface area in one session. And, if the wound area is more than 15 % total body surface area, NexoBrid should be applied in two separate sessions. However, it should not exceed application to more than (b) (4) *% total body surface area.*

In the present study (Study # MW2010-03-02, QT sub-study), the mean % total body surface area of total wounds was 6.28 ± 3.68% for patients in the NexoBrid treatment arm and 6.53 ±3.60 % in the gel vehicle arm. The mean total body surface area total

wound application coverage of ~6.28% in the study is ~42% of what the sponsor is describing in their product label (15% TBSA for one session of drug application; 6.28 / 15 ~ 0.42 %).

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Mediwound Ltd is developing NexoBrid which is a sterile concentrate of proteolytic enzymes enriched in bromelain for the treatment of eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns. The mechanism of the action of NexoBrid is mediated by the proteolytic activity of its enzymes whereby there is selective debridement (i.e., removal of damaged tissue) of eschar or denatured collagen. NexoBrid consists of a complex mixture of natural components of botanical origin (proteolytic enzymes) extracted from pineapple stems (Ananas comosus).

NexoBrid is comprised of two components – 1) 2 (or 5) grams of NexoBrid sterile lyophilized powder mixed with 2) 20 (or 50) grams of sterile gel vehicle per 1% (or 2.5%) total body surface area (TBSA) to achieve a final concentration of (b) (4) grams/gram (1:10 ratio). The sponsor highlights that NexoBrid should not be applied to more than 15% TBSA in one session and if the wound area is more than 15% TBSA then it should be applied in two sessions not to exceed application to more than (b) (4)% TBSA. The expected high clinical exposure scenario is treating (b) (4)% TBSA of a subject treated in 2 consecutive applications of 15% TBSA each. The maximum tolerated dose for repeated application has not been determined.

The peak concentrations of 200 ± 184 ng/mL (Tmax: ~4 h; Half-life ~12 to 17 h) are expected with the anticipated therapeutic dose (Study # MW2010-03-02). Sponsor claims that NexoBrid undergo proteolytic degradation without significant metabolism by the CYP450 enzymes and highlights that it has a low drug interaction potential as a victim drug. The effect of intrinsic factors like age, sex, race, hepatic, and renal impairment have not been determined.

Previously, the IRT reviewed under IND-065448 agreeing that a thorough QT study is not required for NexoBrid (reviews dated 10/12/2012 and 11/16/2018 in DARRTS). Subsequently, the sponsor planned to evaluate the QT effects of their product in a sub-study using Concentration-QT analysis (Study # MW 2010-03-02). This was a multicenter, multinational, randomized, controlled, assessor blinded study performed in subjects with thermal burns to evaluate the safety and efficacy of NexoBrid compared to the gel vehicle and to the standard of care (SOC - surgical and/or nonsurgical procedures). For the clinical study 175 subjects were randomized in a 3:3:1 ratio of NexoBrid, SOC and gel (placebo). Fifteen minutes before application to the burn 2 or 5 grams of NexoBrid sterile powder were mixed with 20 grams or 50 grams of sterile vehicle gel (ratio of 1:10), per 1 % or per 2.5 % TBSA, respectively. Triplicate ECGs were planned on day 1 at -60, -40, -20 minutes pre-dose, at 0.5, 2, 4 hours from the start of the first treatment and at 12, 24, 48 hours. Pharmacokinetic sampling was planned at pre-dose and at 0.5, 1, 2, 4, 12, 24, 48 and 72

hours after the first treatment of NexoBrid is applied. Refer to the IRT review under IND-065448 dated 11/16/2018 in DARRTS.

3.1.2 Nonclinical Safety Pharmacology Assessments

NexoBrid is a complex mixture of a concentrate of proteolytic enzymes enriched in Bromelain extracted from pineapple stems. The sponsor did not include summary of nonclinical assessment in the submitted the highlights of clinical pharmacology and clinical safety (Refer to m2.6.4).

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for NexoBrid was based on exposure-response analysis in the submission, please see section 3.2.3 for additional details. The sponsor provided supportive descriptive statistics to describe by time profiles of ECG variable parameters change from baseline. No large effect was concluded by sponsor's by-time descriptive statistics summary on change from baseline QTcF.

Reviewer's comment: The reviewer's assessment considered by-time analysis as primary. The analysis was based on a linear mixed-effects model and the by-time profiles were assessed based on placebo adjusted mean change from baseline. The reviewer's analysis also does not show large effect. Please see section 4.3 for more details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: Sponsor's QTcF, PR, QRS results are consistent with reviewer's results. Sponsor's HR outlier counts include > 25% change from baseline criteria which is different from the criterion used by the reviewer. Please see section 4.4.2 for details.

3.2.3 Exposure-Response Analysis

The sponsor explored the PK/PD relationship between the change from baseline in QTc interval (ΔQTcF) and the serum concentration of NexoBrid using linear mixed mixed-effects model. The model included serum concentration of NexoBrid, time, treatment, intercept and subject were included as random effects.

The sponsor's analysis shows that there was a slight positive slope of 0.0248 msec/ng/mL (p-value 0.2149 not statistically significant) for the relationship between ΔQTcF and serum concentration of NexoBrid. Based on the linear model the predicted ΔQTcF was 4.96 msec

(upper 90% CI 9.93 msec) at the mean Cmax of 200 ng/mL. The Sponsor's analysis indicates an absence of significant QTc prolongation upon application of NexoBrid.

Reviewer's comment: The conclusion of the reviewer's analysis agreed with the sponsor's analysis. However, NexoBrid is a complex mixture of a concentrate of proteolytic enzymes with multiple components and the reviewers conducted by-time analysis as primary analysis. Please see Section 4.5 for details.

3.2.4 Safety Analysis

Overall, 175 patients were randomized into the DETECT study (NexoBrid: 75, SOC: 75, and Gel Vehicle: 25) and 169 patients were treated (NexoBrid: 77, SOC, 68, and Gel Vehicle (24).

The analysis of AEs was based on the SAS consisting of 77 patients treated with NexoBrid, 68 patients with SOC, and 24 patients with Gel Vehicle.

In the Acute Phase, 47/77 (61.0%) patients treated with NexoBrid, 39/68 (57.4%) patients treated with the SOC, and 15/24 (62.5%) patients treated with the Gel Vehicle reported at least 1 AE following randomization. Most of the AEs were mild to moderate; severe AEs were reported by 10 patients (4 treated with NexoBrid, 3 with the SOC, and 3 with the Gel Vehicle). Serious AEs were reported by 6 patients treated with NexoBrid, 4 patients treated with the SOC, and 3 patients treated with the Gel Vehicle. Nine patients treated with NexoBrid had at least 1 AE reported as possibly related, probably related, or related to study drug. ne death was reported; a patient treated with NexoBrid (Table 36).

For the 12M FU Period, all AEs reported were TEAEs.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, significant ventricular arrhythmias or sudden cardiac death) occurred in the treatment group.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 0).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG on Day 1.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes an unstructured covariance matrix to explain the associated between repeated measures within treatment.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTc for different treatment groups. The maximum ΔΔQTc values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).

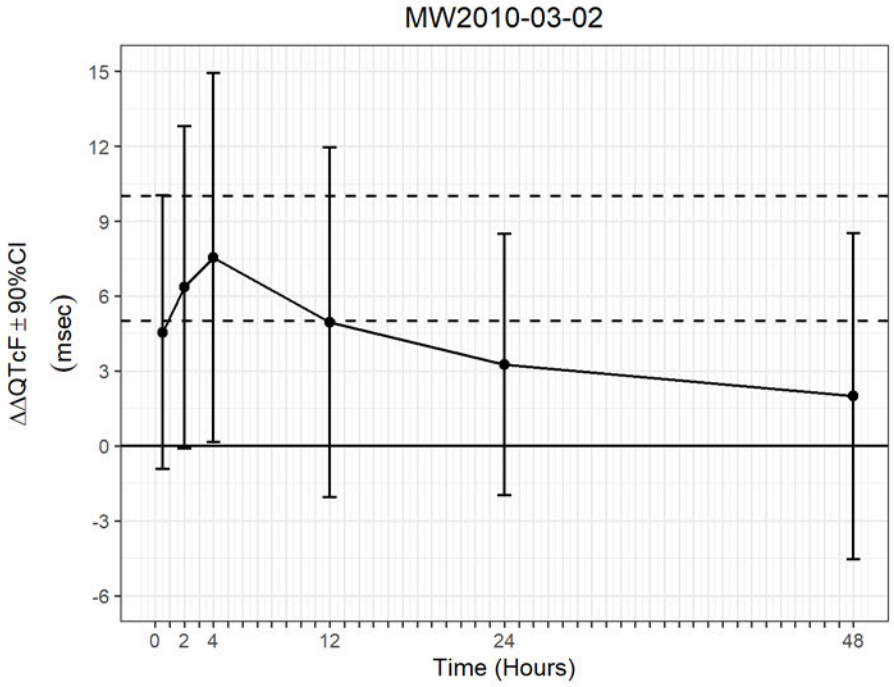


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTc

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTcF (msec)	90.0% CI (msec)
Topical:NexoBrid Gel	54 / 17	4.0	7.5	(0.2 to 14.9)

4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups. The maximum ΔΔHR values by treatment are shown in Table 3.

Figure 2: Mean and 90% CI of ΔΔHR Timecourse

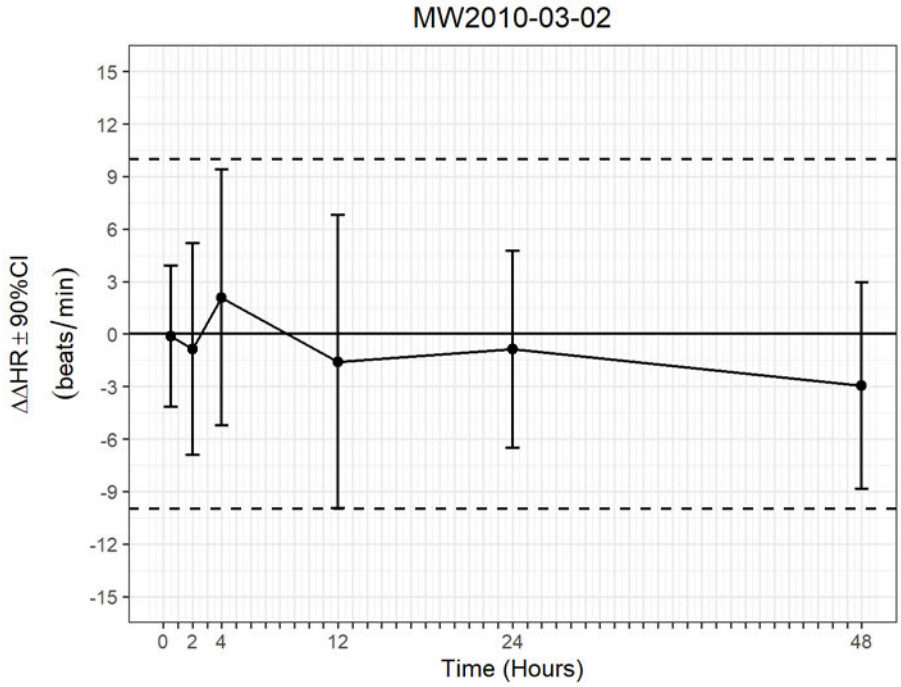


Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔHR

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔHR (beats/min)	90.0% CI (beats/min)
Topical:NexoBrid Gel	54 / 17	4.0	2.1	(-5.2 to 9.4)

4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups. The maximum ΔΔPR values by treatment are shown in Table 4.

Figure 3: Mean and 90% CI of ΔΔPR Timecourse

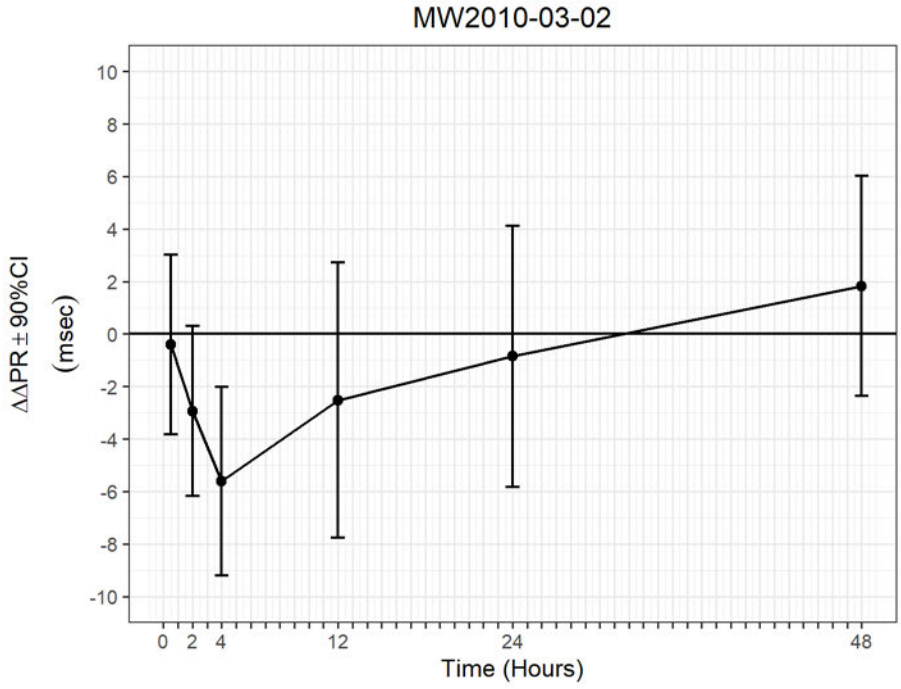


Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔPR

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔPR (msec)	90.0% CI (msec)
Topical:NexoBrid Gel	46 / 13	48.0	1.8	(-2.4 to 6.0)

4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups. The maximum ΔΔQRS values by treatment are shown in Table 5.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse

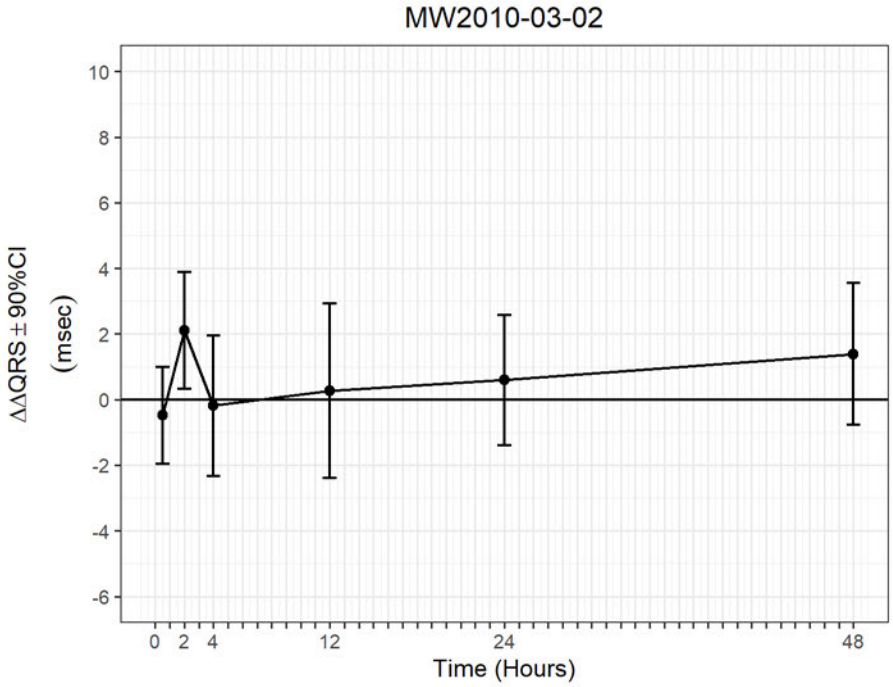


Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQRS

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQRS (msec)	90.0% CI (msec)
Topical:NexoBrid Gel	53 / 18	2.0	2.1	(0.3 to 3.9)

4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs on Day 1.

4.4.1 QTc

None of subjects received NexoBrid gel experienced QTcF above 480 msec or ΔQTcF above 60 msec.

4.4.2 HR

Table 6 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). About 47.3% of subjects received NexoBrid gel experienced HR greater than 100 bpm and the maximum observed HR from subject (# (b) (6) in NexoBrid arm was above 150 bpm. Both treatment and placebo arms had more outliers around 2 to 4 hours.

Table 6: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Topical:NexoBrid Gel	55	334	29 (52.7%)	271 (81.1%)	26 (47.3%)	63 (18.9%)
Topical:Gel Vehicle	19	97	13 (68.4%)	87 (89.7%)	6 (31.6%)	10 (10.3%)

4.4.3 PR

None of subjects received NexoBrid gel experienced PR above 220 msec with corresponding change from baseline above 25%.

4.4.4 QRS

None of subjects received NexoBrid gel experienced QRS above 120 msec with corresponding change from baseline above 25%.

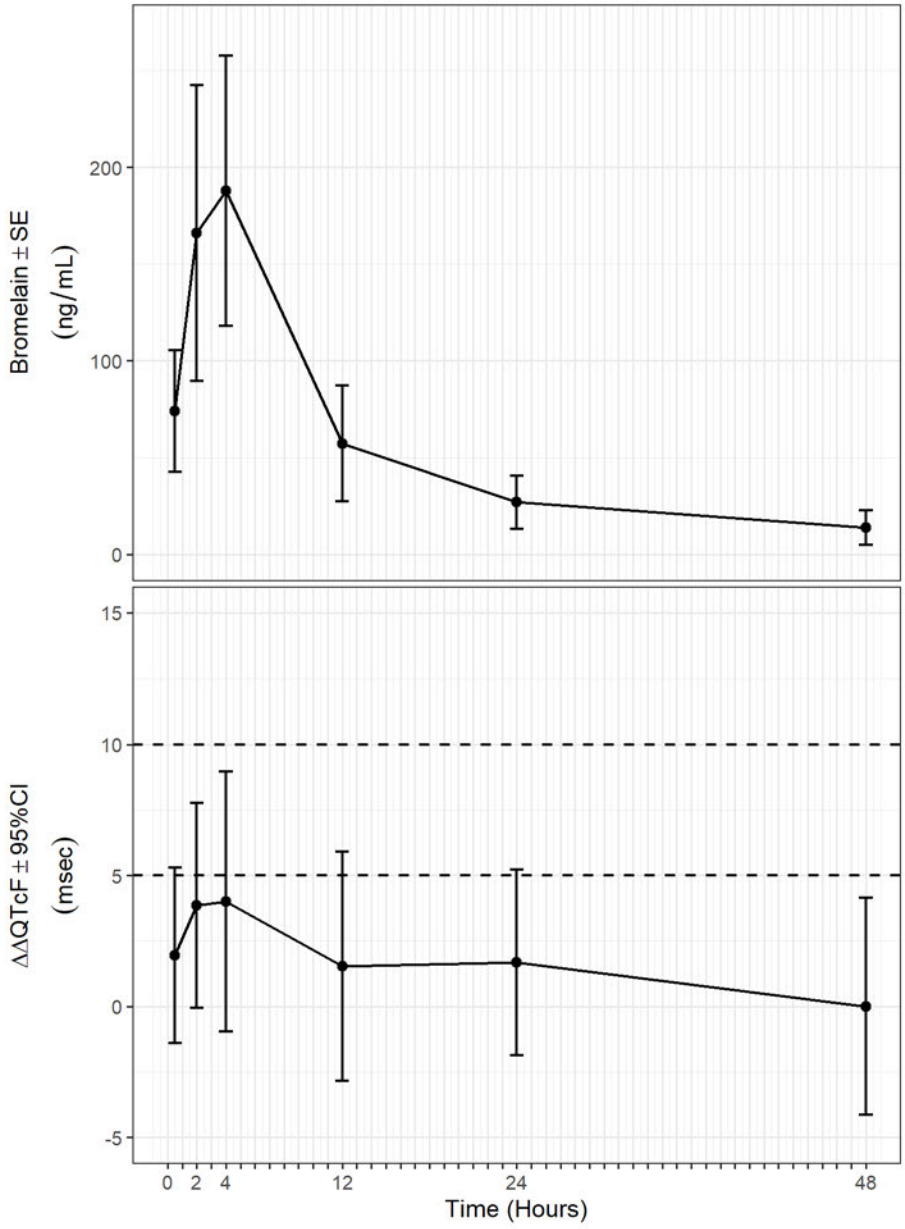
4.5 EXPOSURE-RESPONSE ANALYSIS

NexoBrid is a complex mixture of a concentrate of proteolytic enzymes with multiple components (enriched in Bromelain). For this purpose, the reviewers conducted by-time analysis as primary analysis (see Section 4.3). In addition, the exposure-response analysis was conducted as a supportive analysis using serum Bromelain concentrations (refer to Clinical Pharmacology Review for bioanalysis of bromelain).

The objective of the clinical pharmacology analysis was to assess the relationship between serum concentration of bromelain and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

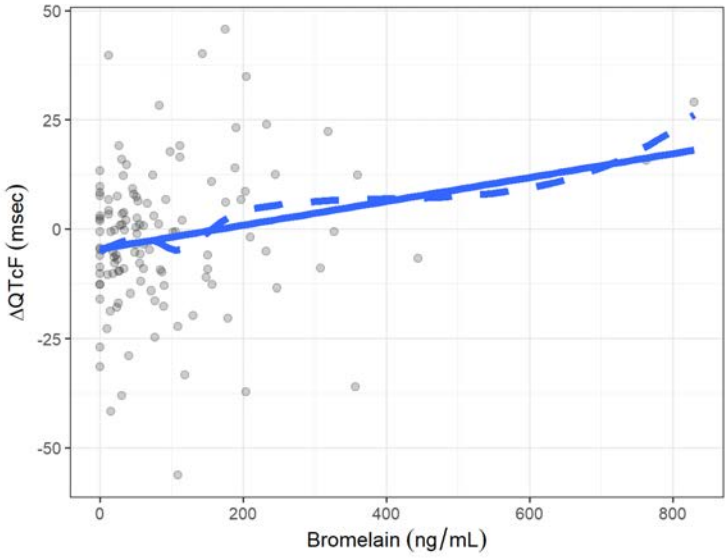
Prior to evaluating the relationship between bromelain serum concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between bromelain concentration and ΔΔQTc and 3) presence of non-linear relationship. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and Figure 5 evaluates the time-course of bromelain concentration and ΔΔQTc and do not appear to show significant hysteresis.

Figure 5: Time course of bromelain concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between bromelain concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between bromelain concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of bromelain concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 7.

Figure 7: Goodness-of-fit plot for QTc

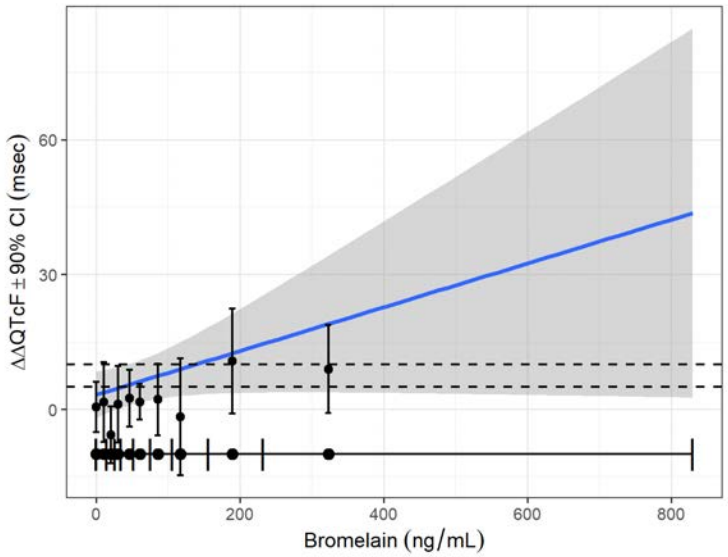


Table 7: Predictions from concentration-QTc model

Actual Treatment	Analysis Nominal Period Day (C)	Bromelain (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
NexoBrid Gel (Topical Application)	1	151.8	10.6	(3.4 to 17.9)

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/s/

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DALONG HUANG
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MICHAEL Y LI
12/02/2020 12:41:37 PM

CHRISTINE E GARNETT
12/02/2020 12:59:38 PM

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

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

Memorandum

Date: November 29, 2022

To: Jennifer Harmon, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Brenda Carr, Clinical Reviewer, DDD

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for NEXOBRID® (anacaulase-xxxx) for topical gel

BLA: 761192

Background:

In response to DDD's consult request dated November 17, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for Nexobrid.

PI

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 17, 2022, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on November 29, 2022, and we do not have any comments at this time.

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

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

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DAVID F FOSS
11/29/2022 04:49:06 PM

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

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

Memorandum

Date: November 3, 2022

To: Jennifer Harmon, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Brenda Carr, M.D. DDD

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for NEXOBRID (anacaulase-xxxx) topical gel

BLA: 761192

Background:

This memo is in response to DDD's labeling consult request dated August 3, 2020. OPDP defers comment on the proposed labeling at this time, and requests that DDD submit a new consult request during the subsequent review cycle. If you have any questions, please contact David Foss at 240-402-7112 or David.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
11/03/2022 12:39:21 PM

Clinical Inspection Summary

Date	18 May 2021
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jennifer Harmon, Pharm.D., RPM Brenda Carr, MD, Medical Reviewer Snezana Trajkovic, MD, Medical Team Leader Division of Dermatology and Dentistry (DDD)
BLA #	761192
Applicant	MediWound, Ltd.
Drug	NexoBrid (concentrate of proteolytic enzymes enriched in Bromelain)
NME	Yes
Proposed Indication	For eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.
Consultation Request Date	5 August 2020
Summary Goal Date	15 June 2021
Action Goal Date	31 May 2021
PDUFA Date	29 Jun 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Routine PDUFA inspections of 3 clinical investigators, Drs. Blome-Eberwein, Goverman, and Singer, were conducted in support of this application (BLA 761192). In addition, the results of for-cause inspections of two clinical investigators, Drs. Singer and Mullins (conducted before submission of this BLA), are included in this Clinical Inspection Summary (CIS). The inspections covered one clinical study, MW2010-03-02. Based on the very significant inspectional observations as described below, OSI has concerns regarding the reliability of the efficacy and safety endpoint data for Protocol MW2010-03-02.

Significant concerns related to the (b) (4)

(b) (4)

(b) (4)

implemented at the sites to minimize bias in the efficacy and safety assessments. All of the protocol-required measures that sites were to implement to minimize bias and to maintain blinding of the assessors are further described in Section II of this CIS. Among the many measures, the protocol required that study staff be identified to serve in unblinded roles to perform standard of care procedures and certain protocol-specific procedures, such as pharmacokinetic (PK) and immunogenicity sampling (performed only in subjects randomized to NexoBrid) and the prescribing, dispensing, and application of the topical products. The protocol required other study staff to serve in a blinded role as a first or second blinded assessor to perform the eschar removal assessments and the main safety assessments (e.g., weekly assessments for wound closure and long term cosmesis as well as some functionality assessments). The first blinded assessors evaluated eschar removal and were blinded to the topical arms only (i.e., they were unblinded to SOC arm). The second blinded assessors performed the main safety assessments and were blinded to all three study arms.

Protocol-required measures necessary to minimize bias in the efficacy and safety assessments and to maintain the blinding of the assessors were not followed at the sites inspected, which resulted in the occurrence of unblinding events in 36 of 43 (84%) randomized subjects at the four sites. Unblinding of the blinded assessors occurred in a variety of ways and are described in more detail in Section III of the CIS.

Also noted at all four sites inspected was the use of photographs in lieu of protocol-required live assessments in many subjects to assess eschar removal and wound closure. In a 26 Jan 2021 sponsor response to an Information Request (IR), the sponsor submitted a list of eschar removal and wound closure assessments made using photographs, which per the sponsor occurred at 9 of the 27 sites. The sponsor's listing provided in the 26 Jan 2021 response was verified against all occurrences of eschar removal and wound closure assessments made using photographs that were noted in the inspection reports and the collected exhibits. The following additional cases were observed that were not reported in the 26 Jan 2021 sponsor response:

(b) (4)

In addition, at Dr. Singer's site, there was no training documented for one first blinded assessor and five second blinded assessors prior to their start of the wound assessments. There was also no training documented for two second blinded assessors.

Of note, during the routine PDUFA inspections, the source data for the primary efficacy endpoint (i.e., complete eschar removal), a key secondary endpoint (i.e., blood loss), and a safety endpoint of interest (i.e., time to wound closure) were verified against the sponsor's data

line listings for the 38 randomized subjects at Sites 0103 (n=9), 0104 (n=21), and 0117 (n=8). One single discrepancy was noted at Site 0117 in a secondary efficacy endpoint of time to complete eschar removal.

While the sponsor's data line listings for the primary and key secondary efficacy endpoints and safety endpoint of interest were verifiable (i.e., the sponsor's data line listings matched what was reported in the source records at the sites), the eschar removal (i.e., primary efficacy endpoint) and wound closure (i.e., safety endpoint of interest) assessments made by the first and second blinded assessors in the study do not appear to be reliable because of the following:

- The potential for the introduction of bias in the assessments of eschar removal and wound closure due to first and second blinded assessor unblinding events that occurred in 84% of subjects randomized at the four sites inspected.
- The failure of the clinical investigators to follow the protocol by using photographs in many cases to evaluate eschar removal and wound closure in lieu of the protocol-required live assessments
- The lack of training of the blinded assessors noted at Dr. Singer's site

In summary, this study was not conducted in accordance with the protocol and current Good Clinical Practice (GCP) standards. The quality of the data generated from the study are of poor quality, and OSI recommends that the study data be evaluated as if they were obtained from an open label study.

II. BACKGROUND

BLA 761192 was submitted in support of the use of NexoBrid for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns. The key study supporting the application was the following:

- MW2010-03-02, "A multicenter, multinational, randomized, controlled, assessor blinded study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid compared to Gel Vehicle and compared to Standard of Care"

This was a multicenter, randomized, controlled, assessor-blinded, 3-arm study designed to demonstrate the superiority of NexoBrid treatment over a Gel Vehicle control and standard of care (SOC) treatment in subjects with thermal burns.

- ***Subjects:*** A total of 175 subjects were randomized (75 subjects in NexoBrid arm, 75 subjects in the SOC arm, and 25 subjects in the Gel Vehicle arm)

- ***Sites:*** 27 sites in the United States, Eastern and Western Europe, and Israel

- ***Study Initiation and Completion Dates:*** 27 May 2015 to 03 September 2019

- ***Database Lock Date:*** 6 Sep 2019

The study objectives were:

- To demonstrate the efficacy of enzymatic eschar removal with NexoBrid by providing complete eschar removal as compared with Gel Vehicle
- To demonstrate the efficacy of enzymatic eschar removal with NexoBrid by providing earlier complete eschar removal, reduction in subjects' surgical burden, and reduction in related blood loss as compared to SOC
- To assess the safety of NexoBrid compared to SOC, including demonstration that treatment with NexoBrid does not cause an unacceptable level of harm on wound closure outcome and long-term outcomes of cosmesis and function

At the Screening and Baseline Visit, physicians identified one or more target wounds (i.e., burn areas to be treated) per subject according to the target wound definitions described in the protocol. Eligible subjects were stratified according the following:

- Total body surface area of burn (in percentage): less than or equal to 15% or greater than 15%
- Overall depth of target wound: all target wounds were FT; mixed target wounds (i.e., FT and DPT); or all target wounds were DPT
- Treatment Center Group: 5 groups of treatment centers were formed based on similarity of SOC practice

After stratification, subjects were randomized in a 3:3:1 ratio to NexoBrid, SOC, or Gel Vehicle. Subjects in all treatment arms received similar care except for the eschar removal stage, which was to be performed as per the randomization treatment arm. All of a subject's DPT and FT burns that met the specified entry criteria were defined as target wound and were to receive study treatment per the randomized treatment arm. The total duration of the study treatment and follow-up period for each subject was expected to be approximately 25 months.

Eschar removal procedure was initiated at the end of the cleansing and blister removal session (debridement), after wound soaking. Topical product was applied by a health care professional to the wound within 15 minutes of mixing and left on for a 4-hour period. After 4 hours, the wound bed with the remains of the dissolved eschar and topical agent was wiped away, and the wound bed was soaked for an additional 2 hours to remove any remains of the mixture. Following removal of the soaking dressing (6 hours of treatment in total), the wound bed was photographed in a standardized manner, and the extent of eschar removal was clinically assessed by a blinded assessor.

Following eschar removal procedures, subjects were treated in accordance with post eschar removal wound care strategies and were assessed daily for vital signs and pain until hospital discharge. After hospital discharge, subjects were followed up until complete wound closure was achieved and confirmed and then 2 weeks later for the status of each of the subject's target wounds. Long-term follow up visits were to be performed at 1, 3, 6, 12, 18, and 24 months post last wound closure confirmation visit.

Study Endpoints:

- The ***primary efficacy endpoint*** was the incidence of complete eschar removal (as compared between NexoBrid and Gel Vehicle) at the end of the topical agent

soaking period as assessed by a blinded assessor
- A key ***secondary efficacy endpoint*** of interest was blood loss related to eschar removal (as compared between NexoBrid and SOC)
- An important ***safety endpoint of interest*** was time to reach complete wound closure assessed in days, as assessed by a blinded assessor, starting from the randomization date

Measures Taken to Minimize Bias:

The topical arms were impossible to disguise in terms of preparation procedures and appearance, even if supplied in masked containers, because NexoBrid was a gold color gel and the Gel Vehicle was a transparent gel. Therefore, in order to minimize bias in the study results, the protocol required that the application of the topical product (NexoBrid or Gel Vehicle) be performed by an unblinded health care professional while the wound assessments (i.e., efficacy and safety endpoint assessments) be performed by different health care professionals who were blinded to the randomized study arms. Thus, two blinded assessors (i.e., first and second blinded assessors) were used to evaluate eschar removal and the main safety assessments (e.g., weekly assessments for wound closure and long term cosmesis as well as some functionality assessments).

The first blinded assessor evaluated eschar removal in all treatment arms and for all procedures until complete eschar removal but was blinded only to the topical arms (NexoBrid and Gel Vehicle). At any particular site, if feasible, the same first blinded assessor should have been assigned to assess eschar removal in all subjects and in all study arms. The first blinded assessor evaluated eschar removal immediately following removal of the soaking dressing, 6 hours after start of first and second treatment, and after any additional procedures until complete eschar removal. The assessment included photographs, wound depth assessments, and clinical assessments of the extent of eschar removal.

The second blinded assessor was blinded to all treatment arms (NexoBrid, SOC, and Gel Vehicle) and performed the weekly main safety assessments of wound closure and long term cosmesis and function. At any particular study site, if feasible, the same second blinded assessor should have been assigned to assess wound closure, cosmesis, and function in all subjects and all study arms. The second blinded assessor was to do the following:
- Photograph all wounds
- Perform a clinical assessment of percent of target wound area epithelialized and/or closed by graft and assess percent donor site epithelialized
- Perform an assessment 2 to 7 days post-grafting of the percent ‘take’ of any graft
- Complete Patient and Observer Scar Assessment Scale and modified Vancouver Scar Scale
- Perform range of motion measurements of injured and non-injured joints

Both the first and second blinded assessors were required to perform all the above assessments during the subjects' visits as 'live' assessments (i.e., both subject and assessor in same room).

To minimize bias and maintain the blind of the assessors, a designated individual at the treatment center received the treatment allocation. This individual was not permitted to communicate the allocated treatment to the blinded assessors. In addition, because the pharmacokinetic and immunogenicity testing was done only for the NexoBrid subjects, the protocol required that this testing was to be performed by unblinded site staff and be recorded in a separate worksheet for the purpose of keeping the blinded assessors blinded to study arm.

Other protocol-required measures to minimize bias included the following:

- The first blinded assessor should not have been involved with product application
- The second blinded assessor (wound closure and long-term assessor) should not have been involved with any eschar removal procedure
- PK and immunogenicity blood sampling should not have taken place at the same time as the blinded assessment
- The topical (NexoBrid/Gel Vehicle) treatment allocation should not have been accessible through the subject's electronic case report forms (eCRFs)
- Paper source documents that could unblind the blinded assessors were to be kept in a separate folder, appropriately labeled
- The blinded assessor should not have reviewed subject's data, such as randomization reports, PK and immunogenicity blood collection, drug accountability records, and any other data that could unblind the assessor to the topical arms
- All IP (used and unused) should have been stored, dispensed, and administered out of the sight of the blinded assessors
- The weekly and long term follow up set of source worksheets should have been separate sections and should not have revealed the treatment arm
- The second blinded assessor should not have reviewed other sections of source worksheets and should not have accessed the eCRFs

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, high incidence of adverse events, protocol deviations, and prior inspectional history.

III. RESULTS (by site):

1. **Sigrid Blome-Eberwein, MD**
   Site #0103
   Lehigh Valley Hospital/Lehigh Valley Health Network
   Cedar Crest Blvd. & I-78
   Allentown, PA 18103
   PDUFA Inspection Dates: 10, 11, 14, 15, 17, 21, 24, 25, 28 Sep 2020

At this site for Protocol MW2010-03-02, 10 subjects were screened and enrolled (i.e., signed informed consent), 9 were randomized, and 6 subjects completed the study. One subject was determined to be a screen failure after signing informed consent, and 3 subjects were lost to follow-up. Subject (b) (6) was lost to follow-up before the 6-month visit. Subjects (b) (6) and (b) (6) were reported to the site's institutional review board (IRB) as lost to follow-up after the 18-month visit; however, these two subjects were not listed as lost to follow-up in the sponsor's data line listings.

An audit of the study records for the 10 enrolled subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary and key secondary efficacy endpoint data (i.e., complete eschar removal and actual blood loss) and safety endpoints of interest (i.e., time to reach wound closure); adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records for eschar removal and the data elements used to calculate actual blood loss (i.e., primary and key secondary efficacy endpoint data) and time to reach wound closure (i.e., safety endpoint of interest) were reviewed and verified against the sponsor's data line listings for the 9 randomized subjects. No discrepancies were noted.

However, the protocol-required measures necessary to minimize bias and to prevent accidental unblinding of the first and second blinded assessors were not followed. Specifically, unblinding events were noted to have occurred in 5 of the 9 randomized subjects (56%). Table 1 contains a listing and description of these unblinding events that were noted to have occurred at this site. Following the table is an explanation of which assessments were impacted

Table 1: Unblinding Events at Site 0103

Subject Number/ Randomization	Date of Unblinding Event (Study Day)	Description of Unblinding Event(s)	Assessment(s) Impacted	Reported to FDA in Protocol Deviation Listing
(b) (6) NexoBrid	(b) (6) (Day 10)	Unblinded physician acted in the role of second blinded assessor and performed Week 1 FU wound closure assessment	Wound closure	No
(b) (6) SOC	Starting (b) (6) (b) (6) (Day 31)	Immunogenicity question on the study worksheet at Week 4, located in the second-blinded assessor's binder (i.e., information accessible to second blinded assessors) was completed incorrectly, indicating that the collection of immunogenicity samples for these two subjects was not applicable, thus revealing that the subjects were not randomized to NexoBrid	Wound closure	No
(b) (6) SOC	Starting (b) (6) (b) (6) (Day 31)			
(b) (6) NexoBrid	Starting (b) (6) (b) (6) (Day 3)	The physician's progress notes in the subject's medical records revealed subject was randomized to a topical treatment arm	Wound closure	No
(b) (6) Gel Vehicle	Starting (b) (6) (b) (6) (Day 10)	The physician's progress notes in the subject's medical records revealed subject was randomized to a topical treatment arm. In addition, the immunogenicity question on the study worksheet at Week 4 ((b) (6)), located in the second-blinded assessor's binder (i.e., information accessible to second blinded assessors) was completed incorrectly, indicating that the collection of immunogenicity samples for this subject was not applicable, thus revealing that the subject was not randomized to NexoBrid.	Wound Closure	No

Reviewer's comment: *A Form FDA 483 was issued at the end of the inspection noting*

these unblinding events. Dr. Blome-Eberwein acknowledged the potential for unblinding in her response letter dated 7 Oct 2020 and further stated that for Subjects (b) (6) (b) (6) *and* (b) (6) *the second blinded assessors did not have access to the page of the subject-specific study worksheets that contained the immunogenicity sample instructions. However, all pages of the subject-specific study worksheets were noted to have been stored together in the subject's study binder that was accessible to the second blinded assessors. The unblinding events in these subjects (i.e.,* (b) (6) *and* (b) (6) *likely would only impact the wound closure assessments because they occurred at the Week 4 visit after the eschar removal assessment had been completed. In addition, the unblinding event noted in Subject* (b) (6) *would only impact this subject's Week 1 wound closure assessment because this was the only assessment in this subject noted to have been conducted by an unblinded physician.*

Furthermore, the physician's progress notes, located in the site's EHR and in the study binders as paper printouts, revealed that Subjects (b) (6) *(randomized on* (b) (6) *) and* (b) (6) *(randomized on* (b) (6) *) were randomized to a topical arm and not to SOC. In a 12 Apr 2021 response to an IR, the sponsor noted that individuals who acted as blinded assessors at this site had access to the site's EHR. The sponsor further noted that while the EHRs contained audit trails, the audit trails could not be provided to show if the second blinded assessors accessed a subject's medical record. These unblinding events likely would only have an impact on the wound closure assessments because they occurred after the topical application and eschar removal assessments had been completed in these subjects.*

Eschar removal and wound closure assessments were also noted to have been made using photographs in lieu of the protocol-required live assessments. In a 26 January 2021 sponsor response to an IR, the sponsor provided a listing of assessments made using photographs. The sponsor's listing was verified against all occurrences of eschar removal and wound closure assessments made using photographs that were noted in the inspection reports and the collected exhibits. At this clinical investigator site, no other assessments conducted using photographs were noted in the inspection report other than what the sponsor reported to FDA.

2. Jeremy Goverman, MD
Site #0104
Massachusetts General Hospital
55 Fruit Street
Boston, MA 2114
PDUFA Inspection Dates: 23 to 28 September 2020

At this site for Protocol MW2010-03-02, 22 subjects were screened and enrolled (i.e., signed informed consent), 21 were randomized, and 6 subjects completed the study. Two subjects withdrew consent, and 13 subjects were lost to follow-up during the long-term follow-up phase of the study. During inspection, it was noted that documentation was available showing that the site study personnel made multiple attempts to contact subjects

lost to follow-up.

An audit of the study records for the 22 enrolled subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary and key secondary efficacy endpoint data and safety endpoints of interest (i.e., complete eschar removal, actual blood loss, and time to reach wound closure); adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records for eschar removal and data elements used to calculate actual blood loss (i.e., primary and key secondary efficacy endpoint data) and time to reach wound closure (i.e., safety endpoint of interest) were reviewed and verified against the sponsor's data line listings for the 21 randomized subjects. No discrepancies were noted.

However, the protocol-required measures to minimize bias and to prevent the unblinding of the first and second blinded assessors were not followed. Unblinding events potentially occurred in all 21 randomized subjects at this site because the actual treatment assignments were revealed in the EHR in two separate places (i.e., the medication orders and medication lists). These unblinding events occurred at the time of randomization for each subject.

Reviewer's comment: *In a 12 Apr 2021 response to an IR, the sponsor noted that individuals who acted as blinded assessors at this site had access to the site's EHR. The sponsor further noted that while the EHRs contained audit trails, the audit trails could not be provided to show if the first and second blinded assessors accessed a subject's medical record. These unblinding events would have an impact specifically on the eschar removal assessments for12 subjects randomized to a topical arm (as first blinded assessors were only blinded to the topical arms) and on the wound closure assessments for all 21 randomized subjects (as second blinded assessors were blinded to all three treatment arms).*

Eschar removal and wound closure assessments were also noted to have been made using photographs in lieu of the protocol-required live assessments. The first blinded assessor was interviewed during the inspection and stated that in general all eschar removal assessments were made using photographs at this site. In a 26 Jan 2021 response to an IR, the sponsor provided a listing of assessments that were conducted using photographs. The sponsor's listing was verified against all occurrences of eschar removal and wound closure assessments made using photographs that were noted in the inspection reports and the collected exhibits. At this clinical investigator site, discrepancies with the sponsor's listing were noted as the sponsor's listing indicated that no eschar removal assessments were made using photographs.

Reviewer's comment: *It is not clear how many subjects had their first-blinded*

assessments made using photographs in lieu of live assessments at this site. No other specific information or exhibits were provided in the inspection report to verify the first blinded assessor's statement made during the inspection, that all eschar removal assessments were made using photographs at this site. The blinded assessor's statement is nevertheless noted in this CIS because the assessor's account of the conduct of the study at this site differs greatly from what the sponsor reported in the 26 Jan 2021 response.

3. Adam Singer, MD
Site #0117
Stony Brook Medicine
Department of Emergency Medicine
101 Nicholls Road, UH-L4
Stony Brook, NY 11794
For-cause Inspection Dates: 14 to 17, 21 to 24, 27 February, and 6 March 2017
PDUFA Inspection Dates: 26 August to 2 September 2020

At this site for Protocol MW2010-03-02, per the sponsor's data listings, 8 subjects were screened and enrolled (i.e., signed informed consent), all of whom were randomized, and 5 subjects completed the study. Two subjects were lost to follow-up and one subject early terminated for unspecified reasons during the long-term follow-up phase of the study.

For-cause and PDUFA inspections of Dr. Adam Singer were conducted to evaluate the conduct of Protocol MW2010-03-02. The for-cause inspection took place in 2017, during the conduct of the Protocol MW2010-03-02, in response to an April 2016 IRB report to the FDA. The IRB reported multiple incidents of GCP noncompliance, including numerous study tests and assessments performed late or not at all, unblinding of first and second blinded assessors, and dosing errors. The focus of the for-cause inspection was to follow-up on the IRB report and included an audit of the study records for the 7 subjects who had been enrolled at that time.

The PDUFA inspection was conducted after Protocol MW2010-03-02 was completed and the Clinical Study Report had been submitted to FDA. During the PDUFA inspection, an audit of the study record for all 8 randomized subjects was conducted and focused on adverse event reporting, protocol deviations, and verification of the primary and key secondary efficacy endpoint data as well as the safety endpoints of interest. There was also a review of processes and procedures that were in place at the site to ensure that the protocol-required measures to minimize bias were implemented.

Records reviewed during both the for-cause and PDUFA inspections included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s, financial disclosure records); case report forms, adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters. In addition, during the PDUFA inspection, source records related to the primary and key secondary

efficacy endpoint data and safety endpoints of interest (i.e., complete eschar removal, actual blood loss, and time to reach wound closure) were also reviewed.

There was no evidence of under-reporting of adverse events. However, a serious adverse event (SAE) of superficial phlebitis that occurred in Subject (b) (6) on (b) (6) was reported late to the sponsor, on (b) (6) rather than within the 24 hours as required by the protocol.

Reviewer's comment: *A Form FDA 483 was issued at the end of the for-cause inspection that included the late SAE reporting. Dr. Singer acknowledged the late reporting and adequately responded to the inspection finding in a letter dated 17 Mar 2017. This was the only incidence of late reporting of an SAE noted to have occurred at this site and does not impact the safety of the subject or the overall safety results of the study.*

The source records for eschar removal and the data elements used to calculate actual blood loss (i.e., primary and key secondary efficacy endpoint data) and time to reach wound closure (i.e., safety endpoint of interest) were reviewed and verified against the data line listings provided by the sponsor for the 8 randomized subjects. One discrepancy was noted in a secondary endpoint of time to eschar removal for Subject (b) (6) The entire eschar removal period from randomization was documented in the source records to be 9.88 hours or 0.41 days. The sponsor's data line listings report 8.87 hours or 0.37 days.

Reviewer's comment: *This isolated and fairly minor discrepancy in a secondary endpoint of time when complete eschar removal was achieved is not likely to have an effect on the overall efficacy or safety results of the study.*

Furthermore, the protocol-required measures to minimize bias and to prevent the unblinding of the first and second blinded assessors were not followed. Specifically, unblinding events were noted to have occurred in 7 of the 8 (88%) randomized subjects. Table 2 contains a listing and description of the unblinding events that were noted to have occurred at this site. Following the table is an explanation of which assessments were impacted

Table 2: Listing of Unblinding Events at Site 0117

Subject Number Randomization	Date of Unblinding Event (Study Day)	Description of Unblinding Event(s)	Assessment(s) Impacted	Reported to FDA in Protocol Deviation Listing
(b) (6) SOC	Starting (b) (6) (b) (6) (Day 1)	Unblinded staff performed all first and second blinded assessments	Eschar removal and wound closure	No
(b) (6) Gel Vehicle	Starting (b) (6) (b) (6) (Day 1)			Yes
(b) (6) NexoBrid	Starting (b) (6) (b) (6)			Yes, for unblinding of

	(Day 1)			the first blinded assessor; no for unblinding of the second blinded assessor
(b) (6) SOC	(b) (6) (Day 44)	First blinded assessor performed second blinded assessments	Wound Closure	No
(b) (6) NexoBrid	Starting (b) (6) (Day 1)	1. The nurses' progress notes revealed the subject was randomized to NexoBrid. 2. Worksheets, located in a study binder accessible to the first blinded assessors, were completed incorrectly, indicating the collection of PK samples was completed and thus revealing the subject was randomized to NexoBrid.	Eschar removal and wound closure	No
(b) (6) NexoBrid	Starting (b) (6) (Day 2)	The nurses' progress notes revealed subject was randomized to NexoBrid	Eschar removal and wound closure	No
(b) (6) NexoBrid	Starting (b) (6) (b) (6) (Day 44)	Worksheets, located in a study binder accessible to the second blinded assessors, were completed incorrectly, indicating the collection of immunogenicity samples at Week 4 and thus revealing the subject was randomized to NexoBrid	Wound Closure	No

Reviewer's comment: *Unblinded physicians made all first and second blinded assessments up to 14 Jul 2016 for Subjects* (b) (6) *Of note, another second-blinded assessor was assigned on 14 Jul 2016 to perform the second-blinded assessments, and reassessed, up to a year later by using photographs, all previous wound closure assessments made by the unblinded physicians in these 3 subjects.*

The unblinding events for Subjects (b) (6) *(randomized on* (b) (6) *) and* (b) (6) *(randomized* (b) (6) *) would likely impact the reliability of all of the eschar removal and wound closure assessments because they occurred at randomization.*

In addition, the second unblinding event that occurred in Subject (b) (6) *and the unblinding event for Subject* (b) (6) *would only likely impact the reliability of the wound closure assessment because they occurred at Week 4, after the topical application and eschar removal assessment had been completed.*

Eschar removal and wound closure assessments were also noted to have been made using photographs in lieu of the protocol-required live assessments. In a 26 Jan 2021 response to an IR, the sponsor provided a listing of assessments that were conducted using photographs. The sponsor's listing was verified against all occurrences of eschar removal and wound closure assessments made using photographs that were noted in the inspection reports and the collected exhibits. At this clinical investigator site, one additional eschar removal assessment for Subject (b) (6) (randomized to NexoBrid) on (b) (6) that was not reported in the sponsor's listing was noted to have been made using photographs.

There was also no assessor training documented for one first blinded assessor and five second blinded assessors prior to their start of the wound assessments. In addition, there was no training documented at all for two second blinded assessors.

Reviewer's comment: *A Form FDA 483 was issued at the end of the for-cause inspection noting the lack of training for first and second blinded assessors. Dr. Singer acknowledged the lack of training and adequately responded to the inspection finding in a letter dated 17 Mar 2017.*

In addition, issues related to the clinical investigator's and study staff's failure to follow the protocol and other GCP noncompliance issues were noted during the for-cause inspection and included the following:

- Minor NexoBrid dosing errors in Subjects (b) (6)
- Use of normal saline instead of hypertonic saline or an antibacterial solution (as required by the protocol) during the soaking stages prior to and post-treatment in order to minimize the potential for infection and associated fever in Subjects (b) (6) (b) (6) (b) (6) (b) (6) and (b) (6)
- Inadequate drug preparation and accountability records with respect to the time of drug preparation in relation to the times of the treatment procedures, including documentation that identified the study staff who participated in the preparation and the supplies that were used. Specifically, the protocol required that NexoBrid be prepared by designated study staff at the patient bedside less than 15 minutes prior to use. The NexoBrid preparation (including the time of preparation) was not documented for Subjects (b) (6) (b) (6) (b) (6) and (b) (6) (all were randomized to NexoBrid).

Reviewer's comment: *A Form FDA 483 was issued at the end of the for-cause inspection that included the above issues. Dr. Singer acknowledged these protocol deviations and other issues of GCP noncompliance and adequately responded to them in a letter dated 17 Mar 2017. These issues point to larger problems at this site with regard to overall protocol nonadherence and possible lack of understanding of the protocol.*

4. **Robert F. Mullins, MD**
   Site #0120
   Joseph M. Still Burn Center
   3651 Wheeler Rd
   Augusta, GA 30909
   For-cause inspection Dates: 15 to 26 April 2019

At this site for Protocol MW2010-03-02, 5 subjects were screened and enrolled (i.e., signed informed consent), all of whom were randomized, and one subject completed the study. Three subjects were lost to follow-up (i.e., one subject during the long-term follow-up stage of the study and two during the acute phase of the study) and one subject terminated early for unspecified reasons during the acute phase of the study. A for-cause inspection was conducted in response to a report of GCP noncompliance from the IRB. Specifically, the IRB reported that an April 2016 site monitoring visit by a CRO resulted in several critical observations that the CRO believed indicated a lack of clinical investigator oversight, a possible lack of understanding of the protocol, nonadherence to the protocol, and insufficient staff to conduct the study.

During the for-cause inspection, an audit of the study records for the 5 randomized subjects was conducted. Records reviewed included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s, financial disclosure records); case report forms, adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

The protocol-required measures to minimize bias in the efficacy and safety assessments and to prevent unblinding of the first and second blinded assessors were not followed at this site. Specifically, unblinding events were noted to have occurred in 3 of the 5 (60%) randomized subjects. Table 3 contains a listing and description of the unblinding events that were noted to have occurred at this site. Following the table is an explanation of which assessments were impacted

Table 3: Listing of Unblinding Events at Site 0120

Subject Number/ Randomization	Date of Unblinding Event (Study Day)	Description of Unblinding Event(s)	Assessment(s) Impacted	Reported to FDA in Protocol Deviation Listing
(b) (6) NexoBrid	Starting (b) (6) (Day 1)	Physician's progress notes in the EHR revealed subject received NexoBrid. In addition, the clinical research progress notes revealed that the subject was randomized to a topical arm.	Eschar removal and wound closure	No
(b) (6)	Starting (b) (6)	Physician's progress notes in	Wound closure	No

SOC	(b) (6) (Day 1)	the EHR revealed subject consented to the study and SOC		
(b) (6) NexoBrid	Starting (b) (6) (b) (6) (Day 2)	Baseline Pre-treatment and Topical Arms first application worksheets accessible to the first blinded assessors were completed incorrectly indicating that the collection of PK and immunogenicity samples had been completed, revealing subject was randomized to NexoBrid.	Eschar removal	No

Reviewer's comments: *The unblinding event for Subject (b) (6) (randomized on (b) (6) (b) (6)) would likely impact the reliability of both the eschar removal and wound closure assessments because the unblinding event occurred at randomization. The unblinding event for Subject (b) (6) (randomized on (b) (6)) likely would only impact the reliability of the wound closure assessment because the second blinded assessors were supposed to be blinded to all three arms (NexoBrid, Gel Vehicle, and SOC), while the first blinded assessors were only supposed to be blinded to topical arms (NexoBrid or Gel Vehicle). In addition, the unblinding event that occurred in Subjects (b) (6) would only impact the eschar removal assessments because the study worksheets that were completed incorrectly were stored in a binder accessible to first blinded assessors.*

Eschar removal and wound closure assessments were also noted to have been made using photographs in lieu of the protocol-required live assessments. In a 26 January 2021 response to an IR, the sponsor provided a listing of assessments conducted using photographs. The sponsor's listing was verified against all occurrences of eschar removal and wound closure assessments made using photographs that were noted in the inspection reports and the collected exhibits. At this clinical investigator site, the following additional assessments were made using photographs that were not reported in the sponsor's listing

- (b) (6)
-
-

In addition, two of the 5 subjects (40%) were enrolled and randomized at this site with a questionable history of alcohol or drug abuse. Subject (b) (6) had a past medical history of methamphetamine use and was noted to have been burned secondary to a methamphetamine lab explosion. In addition, Subject (b) (6) s medical record noted that the subject was burned from hot water secondary to passing out in the shower from alcohol intoxication.

Reviewer's comment: *Exclusion criteria #25 of the protocol (Version 9, dated 12 Aug 2015) states that subjects with current (within 12 months prior to screening) alcohol abuse (daily consumption >3 units for males and >2 units for females) or drug abuse should be excluded*

from participation. Version 9 of the protocol used the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for substance abuse. Although the protocol did not require that subjects be screened for drugs of abuse prior to their participation in the study, the clinical investigator did not do his due diligence to address and document that Subject (b) (6) *was not currently using methamphetamine. In addition, based on Subject* (b) (6) *s presentation, this subject likely met the DSM-IV alcohol abuse criteria and should have also been excluded.*

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
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OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

APPEARS THIS WAY ON ORIGINAL

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/

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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:	February 23, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761192
Product Name, Dosage Form, and Strength:	NexoBrid (core name -xxxx)[a] for topical gel, 2 g and 5 g [b]
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	MediWound, Ltd
FDA Received Date:	June 29, 2020 and October 2, 2020
OSE RCM #:	2020-1350
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

[a] The proposed nonproprietary name for this product at the time of this review is pending. We therefore refer to the proposed product as "core name-xxxx" throughout this review in place of the nonproprietary name for this product.

[b] The proposed strength statement for this product is under review. We note the Applicant submitted the strengths as 2 g and 5 g for this product.

1 REASON FOR REVIEW

As part of the approval process for NexoBrid (core name -xxxx) for topical gel, the Division of Dermatology and Dentistry (DDD) 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 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), container labels, and carton labeling. We note the PI can be improved to place adequate space between the numerical dose and vial size and unit of measure ((b) (4)). We also note reference to a website for training materials in the Dosage and Administration section and recommend a note be added that the additional information has not been evaluated or approved by the FDA. The container labels and carton labeling can be improved to prevent wrong drug/dose errors and wrong technique errors and facilitate product identification.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling for NexoBrid can be improved. We recommend the following be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

1. General Comment:
    1. We note that at the time of this review, OPB's determination for the product strength statements, the proper name and the proposed package type term "(b) (4) (b) (4)" is pending. Ensure that the OPB's determined product strength statements, the proper name and product type term is used throughout the labels and labeling, including container labels and carton labeling.
2. Prescribing Information
    1. Highlights and Dosage Forms and Strengths Sections
        a. To improve readability in the Dosage Forms and Strengths section of the Highlights, place adequate space between the numerical vial size and unit of measure ((b) (4)).
    2. Dosage and Administration Section
        a. To improve readability, place adequate space between the numerical dose and unit of measure ((b) (4)).
        b. (b) (4)
    3. How Supplied/Storage and Handling Section
        a. We note the use of the placeholders 'xxxx-xxxx(b) (4)' and 'xxxx-xxxx(b) (4)' for the National Drug Code (NDC) and recommend replacing these NDC placeholders with the actual NDC when it is determined.

4.2 RECOMMENDATIONS FOR OFFICE OF BIOTECHNOLOGY PRODUCTS (OBP)

1. See 4.1, general comment above.
2. We note that on the container label and carton labeling, the nonproprietary name is placed above the proprietary name, we defer to OBP to determine if this product a non-specified biologic and that the placement of the nonproprietary name is appropriate per 21 CFR610.62 (a).

4.3 RECOMMENDATIONS FOR MEDIWOUND, LTD

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

A. General Comments (Container labels & Carton Labeling)

1. You have presented the proprietary name in a highly stylized lettering font that may decrease the readability of the name. The "D" in NexoBrid as presented may be misinterpreted as such please revise the font so that "D" appears clear.
2. The nonproprietary name for your product is not yet designated. Once the nonproprietary name with a designated suffix has been determined, revise the nonproprietary name to the labels and labeling and submit for our review.
3. The nonproprietary name lacks prominence commensurate with the proprietary name on NexoBrid powder container labels and carton labeling . According to 21 CFR 610.62, the point size and typeface of the proper name is at least as prominent as the point size and type face of the proprietary name. Ensure that the point size and typeface of the proper name is at least as prominent as the point size and type face of the proprietary name (see 21 CFR 610.62). You can achieve this by either increasing the size of the proper name or reducing the size of the proprietary name.
4. To improve readability, place adequate space between the numerical dose and unit of measure (b) (4)).
5. As currently presented the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXXX-X). Replace these NDC placeholders with the actual NDC when it is determined and submit the revised labels and labeling to the Agency for review.
6. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information.
7. Revise and bold the statement "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.
8. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual container label and carton labeling as required per 21CFR 201.25(c)(2). For the container labels, consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[c]

B. Container Labels

1. For the container labels of the gel vehicle, increase the prominence of the words "Gel" so that it is the most prominent word on the label similar to:

[c] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

Gel

For NexoBrid powder for gel

We recommend this to minimize the risk of wrong drug errors where the gel is administered without the drug. Additionally, add the statement *"For drug preparation use only – mix powder and gel prior to application as directed"* to the bottom of the PDP (space permitting) or on the side panel.

2. For the container labels of the gel vehicle, relocate the net quantity to the PDP.
3. Relocate the route of administration to the PDP, as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
4. Decrease the prominence of the statement "Rx Only" as this information appears more prominent than the established name.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for NexoBrid received on June 29, 2020 and October 2, 2020 from MediWound, Ltd.

Table 2. Relevant Product Information for NexoBrid	
Initial Approval Date	n/a
Nonproprietary Name	core name -xxxx [d]
Indication	eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns
Route of Administration	topical
Dosage Form	for topical gel
Strength	2 g and 5 g
Dose and Frequency	NexoBrid can be applied to an area of up to 15% total body surface area (TBSA) in one session. If the wound area is more than 15% TBSA, NexoBrid should be applied in two (2) separate sessions, but should not exceed application to more than (b) (4)% TBSA. The NexoBrid Gel should be prepared at the patient's bedside within 15 minutes of use. • Apply NexoBrid topically to the moistened burn wound using a sterile tongue depressor in a layer that completely covers the burn area at 2 g NexoBrid sterile powder mixed with 20 g sterile Gel Vehicle per 1% TBSA of an adult ((b) (4)3 mm thick layer) up to 15% TBSA.
How Supplied	Carton containing one vial of 2 g powder and one jar 20 g Gel Vehicle Carton containing one vial of 5 g powder and one jar 50 g Gel Vehicle
Storage	Store and transport refrigerated (2-8°C). Do not freeze. Store upright. Store in the original package to protect from light
Container Closure	Each package of NexoBrid includes one single use vial (glass (b) (4) (b) (4)sealed with a rubber ((b) (4) stopper and covered with a cap ((b) (4) of powder and one jar ((b) (4) glass (b) (4) (b) (4)sealed with a rubber stopper and covered with a screw cap ((b) (4) of Gel Vehicle

[d] The Applicant submission states "concentrate of proteolytic enzymes enriched in bromelain".

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,[e] along with postmarket medication error data, we reviewed the following NexoBrid labels and labeling submitted by MediWound, Ltd.

- Container labels received on June 29, 2020
- Carton labeling received on June 29, 2020
- Prescribing Information (Image not shown) received on October 2, 2020, available from \\CDSESUB1\evsprod\bla761192\0009\m1\us\114-labeling\draft\labeling\draft-labeling-text-word.docx

G.2 Label and Labeling Images

Container Labels

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

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MADHURI R PATEL
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SEVAN H KOLEJIAN
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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and Reproductive Medicine
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Division of Pediatric and Maternal Health Review

Date: February 10, 2021 **Date consulted:** August 3, 2020

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

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

To: Division of Dermatology and Dentistry (DDD)

Drug: NEXOBRID (concentrate of proteolytic enzymes enriched in Bromelain) topical gel, (b) (4) (b) (4)

BLA: 761192 (IND 65448)

Applicant: Vericel Corporation

Subject: Pregnancy and Lactation Labeling Formatting and Recommendations

Proposed Indication: for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns

Materials Reviewed:

- June 29, 2020, BLA 761192 submission from Vericel Corporation for NEXOBRID (concentrate of proteolytic enzymes enriched in Bromelain)

Consult Question: "For assistance in reviewing the labeling relevant to maternal health."

INTRODUCTION AND BACKGROUND

On June 29, 2020, Vericel Corporation submitted original Biologics License Application (BLA 761192) for NEXOBRID (concentrate of proteolytic enzymes enriched in Bromelain) topical gel, (b) (4) for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns. The Division of Dermatology and Dentistry (DDD) consulted the Division of Pediatric and Maternal Health (DPMH) on August 3, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- NEXOBRID was granted Orphan Drug Designation on August 20, 2002.
- The US Biomedical Advanced Research and Development Authority (BARDA) has identified NEXOBRID as a critical Medical Countermeasure (MCM) to address the public health emergency associated with (b) (4) (b) (4) under section 319F–2(c)(2)(A)(ii) of the PHS Act.

Table 1. NEXOBRID Drug Characteristics[1]

Drug Class	Proteolytic enzymes enriched in bromelain. Bromelain is found in the stems and fruit of the pineapple plant.
Mechanism of Action	The mixture of enzymes in NEXOBRID dissolves burn wound eschar. The specific components responsible for this effect have not been identified.
Pharmacokinetics	Topical administration results in rapid absorption of NEXOBRID with quantifiable serum concentrations through 48 hours post-dose administration with no quantifiable concentrations after 72 hours in most subjects.

Dose and Administration	• For topical use only
	• NEXOBRID is available in the following presentations:
	  ○ 2g NEXOBRID lyophilized powder mixed with 20 g gel vehicle per 1% TBSA
	  ○ 5g NEXOBRID lyophilized powder mixed with 50 g gel vehicle per 2.5% TBSA
	• Apply NEXOBRID to burn wound of up to 15% total body surface area (TBSA) in a layer of (b) (4)-3 mm. The duration of application is 4 hours. NEXOBRID may be applied a second time to the same area if eschar removal was not complete.
	• If the wound area is more than 15% TBSA, apply NEXOBRID to different portions of the wound in 2 separate sessions, (b) (4) (b) (4)% TBSA (up to a total of (b) (4)% TBSA).
	• NEXOBRID should not be applied to more than (b) (4)% TBSA.

[1] Drug characteristics discussed with review team

Molecular Weight	Heterogenous mixture MW ranges from 18kD to 28kD
Elimination Half-Life	12-17 hours
Adverse Reactions	Pruritus, pyrexia, sepsis

REVIEW

PREGNANCY

Burns in Pregnant Patients

There is a low incidence of serious burns in pregnant women. When a serious burn occurs in a pregnant woman, she is likely to come from a low-income country.[2] In a 6-year cross-sectional study, 39 women (1.88%) were found to be pregnant among 2,067 women with a severe burn injury.[3]

Nonclinical Experience

In embryofetal developmental studies in rats and rabbits, intravenous doses up to 4 and 0.1 mg/kg/day [proper name-xxxx] were administered to pregnant rats and rabbits, respectively, during organogenesis. No significant developmental toxicities were observed in these studies. However, severe maternal toxicities were noted and the tolerable maternal exposure levels were much lower compared with maximum human exposure in clinical setting; however, these studies were conducted with the IV formulation and maternal toxicities expected to be lower with a topical gel preparation. Pre- and post-natal development studies were not conducted as agreed upon between the Division and the sponsor. The reader is referred to the Pharmacology/Toxicology review by Jianyong Wang, DARRTS.

Review of Literature

Applicant's Review of Literature

The applicant did not provide a review of literature; however, DPMH's literature search described below found no data. No pregnancies were reported in the clinical trials and pregnant women were excluded from all clinical trials. The applicant's submission notes that NEXOBRID is not recommended for use in pregnancy because there are no available data to inform a product-associated risk.

DPMH Review of Literature

DPMH conducted a search of published literature using PubMed and Embase regarding concentrate of proteolytic enzymes enriched in Bromelain exposure during pregnancy using the following search terms, "concentrate of proteolytic enzymes enriched in Bromelain and fetal malformations," "concentrate of proteolytic enzymes enriched in Bromelain and spontaneous abortion and miscarriage," "concentrate of proteolytic enzymes enriched in Bromelain and embryo-fetotoxicity." No observational, prospective randomized studies or case reports were found on the use of concentrate of proteolytic enzymes enriched in Bromelain during pregnancy.

[2] Shi Y. Severe burn injury in late pregnancy: a case report and literature review. Burns Trauma. 2012. 3:2.

[3] Rezavand N, Seyedzadeh A, Soleymani A. Evaluation of maternal and foetal outcomes in pregnant women hospitalized in Kermanshah Hospitals, Iran, owing to burn injury, 2003-2008. Ann Burns Fire Disasters. 2012;25:196–9.

In addition, no information was found in Micromedex[4] or Drugs in Pregnancy and Lactation by Briggs and Freeman.[5]

Reviewer comment: There are no available data on the use of concentrate of proteolytic enzymes enriched in Bromelain during pregnancy and no reported pregnancies in clinical trials. See conclusion below for DPMH's opinion on the use of NEXOBRID during pregnancy.

LACTATION

Nonclinical Experience

There are no available nonclinical data with regard to lactation or breastfeeding. Pre- and post-natal development studies were not conducted as agreed upon between the Division and the sponsor.

Review of Literature

The applicant did not provide a review of literature; however, DPMH conducted a search of published literature using PubMed and Embase regarding concentrate of proteolytic enzymes enriched in Bromelain exposure during lactation. No data were found. Also, there are no additional data in Medication and Mothers Milk,[6] or Drugs in Pregnancy and Lactation by Briggs and Freeman.[5]

Reviewer comment: The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Non-clinical fertility studies were not conducted with NEXOBRID.

Review of Literature

The applicant did not provide a review of literature; however, DPMH conducted a search of published literature using PubMed and Embase regarding concentrate of proteolytic enzymes enriched in Bromelain exposure effects on fertility. No data were found.

Reviewer comment: The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Overall, there are no available human data on the use of NEXOBRID during pregnancy. No significant developmental toxicities were observed in animal reproduction studies in rats and rabbits. However, severe maternal toxicities were noted and the tolerable maternal exposure levels were much lower compared with maximum human exposure in clinical setting. DPMH notes that maternal toxicities were observed with the IV formulation and would not expect to see

[4] Bromelain.Truven Health Analytics LLC. Micromedex.
[5] Briggs, GG and Freeman, R., Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk Online version: http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi.
[6] Hale, Thomas. Bromelain. www halesmeds.com

the same results with the topical gel. DPMH does not agree with the applicant's recommendation [redacted] (b) (4) Due to the proposed indication for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns, the likely use of this product in a hospital setting and the low prevalence of severe burns in pregnant women, it would not be feasible to conduct a post-marketing pregnancy study. DPMH does not recommend issuing a PMR for a post-marketing pregnancy study at this time.

Lactation

There are no available human or non-clinical data with regard to NEXOBRID and lactation. Due to the proposed indication for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns and [redacted] (b) (4) the likely use of this product in a hospital setting and the low prevalence of severe burns in pregnant and lactating women, the used of this product in lactating individuals is likely to be low. Therefore, DPMH does not recommend a PMR for a post-marketing lactation study at this time.

Females and Males of Reproductive Potential

There are no available human or animal data to inform on fertility and no recommendations are needed for pregnancy testing or contraception use for this product. Therefore, DPMH recommends subsection 8.3 Females and Males of Reproductive Potential is omitted from NEXOBRID labeling.

LABELING RECOMMENDATIONS

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

DPMH Proposed Pregnancy and Lactation Labeling

[redacted] (b) (4)

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(b) (4)

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.

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CARRIE M CERESA
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MIRIAM C DINATALE
02/10/2021 11:58:05 AM

LYNNE P YAO
02/19/2021 06:37:10 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	January 8, 2021
Reviewer:	Jessica Weintraub, PharmD, BCPS, Safety Evaluator Division of Pharmacovigilance I
Team Leader:	Vicky Chan, PharmD, BCPS, Safety Evaluator Team Leader Division of Pharmacovigilance I
Division Director:	Cindy Kortepeter, PharmD Division of Pharmacovigilance I
Product Name:	NexoBrid (concentrate of proteolytic enzymes enriched in bromelain) gel
Subject:	Foreign postmarketing safety reports with a focus on endotoxemia
Application Type/Number:	BLA 761192
Applicant:	MediWound, Ltd.
OSE RCM #:	2020-1352

****This document contains information obtained by FDA using VigiLyze, a tool for searching VigiBase, the World Health Organization-Uppsala Monitoring Centre's global database of individual case safety reports (ICSRs). The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information included does not represent the opinion of the Uppsala Monitoring Centre or the World Health Organization. Use of VigiBase data in any document or publication, in whole or in part, must be accompanied by this statement.****

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates foreign postmarketing safety reports and the literature for adverse events suggestive of endotoxemia or other serious adverse events reported with the use of NexoBrid (concentrate of proteolytic enzymes enriched in bromelain) gel. The Division of Dermatology and Dentistry (DDD) consulted the Division of Pharmacovigilance (DPV) to review these reports to assist in their evaluation of Biologics License Application (BLA) 761192 for NexoBrid.

We identified a limited number of cases reporting events such as fever, sepsis, multiple organ dysfunction syndrome, bleeding, and coagulation disorders temporally associated with NexoBrid use that could potentially be consistent with endotoxin exposure. Other factors, such as the hypermetabolic state seen in burn patients, burn-induced coagulopathy, infections, and hypersensitivity could also have contributed to the events. We identified cases reporting anaphylaxis with NexoBrid use. Although we cannot rule out the contribution of concomitant medications used around the time of NexoBrid exposure, the Applicant's proposed labeling refers to (b) (4) This is in contrast to the language in the Summary of Product Characteristics for NexoBrid.

DPV does not have recommendations related to endotoxemia. We recommend consideration of modifying the Applicant's proposed labeling for hypersensitivity to describe the potential for anaphylaxis and (b) (4) with NexoBrid use. Assuming that cases of anaphylaxis and urticaria were not identified in the clinical trials currently under review, we also recommend adding anaphylaxis and urticaria to the *Postmarketing Experience* subsection of ADVERSE REACTIONS. See Section 6 for DPV's proposed language for labeling recommendations.

1 INTRODUCTION

This review evaluates foreign postmarketing safety reports and the literature for adverse events suggestive of endotoxemia or other serious adverse events reported with the use of NexoBrid (concentrate of proteolytic enzymes enriched in bromelain) gel. The Division of Dermatology and Dentistry (DDD) consulted the Division of Pharmacovigilance (DPV) to review these reports to assist in their evaluation of Biologics License Application (BLA) 761192 for NexoBrid.

1.1 BACKGROUND

1.1.1 Review Background

NexoBrid is a botanical product made from a mixture of proteolytic enzymes extracted from pineapple *(Ananas comosus)* stems. NexoBrid was first approved by the European Medicines Agency (EMA) in December 2012 and is marketed as a lyophilized powder with a sterile gel vehicle for reconstitution. It is currently marketed in Israel, the Russian Federation, South Korea, Switzerland, and 15 countries in the European Economic Area.[1] NexoBrid was formerly known as Debrase, Debrase Gel Dressing, Debridase, Debriding Gel Dressing, or DGD.[1,2] The Applicant is evaluating the active substance in NexoBrid in a different concentration and formulation under the investigational drug name EscharEx for debridement of hard-to-heal wounds.[1]

On June 29, 2020, the Applicant submitted BLA 761192 for NexoBrid for the proposed indication of eschar removal (debridement) in adults with deep partial thickness and/or full thickness thermal burns. The End of Phase 2 meeting in 2011 included a discussion regarding the Sponsor's inability to develop a valid endotoxins assay because of (b) (4) (b) (4). The Sponsor proposed that release specifications not include endotoxin content.[3] On August 20, 2020, DDD submitted a consult request to DPV to review foreign postmarketing reports of, or suggestive of, endotoxemia.

Bromelain for oral use is currently marketed as a dietary supplement in the United States. From 1961 to 1985, bromelain was marketed for oral use under the trade name Ananase (New Drug Application [NDA] 12527), and Ananase is currently marketed in some countries. The FDA withdrew approval of the NDA for Ananase on the grounds that the Applicant failed to submit substantial evidence of effectiveness for its intended use for the control of edema or inflammation secondary to surgical or accidental trauma, infections, or allergic manifestations.[4]

We evaluated data from VigiBase, the Applicant's submission of individual case safety reports (ICSRs) and periodic safety reports (PSRs), the medical literature, the FDA Adverse Event Reporting System (FAERS), and the EMA. See Section 2 for more details about the databases used. The Periodic Benefit Risk Evaluation Report (PBRER) for NexoBrid, covering December 18, 2018 to December 17, 2019, that was submitted with the BLA, indicated that the Applicant's postmarket safety database included approximately 150 ICSRs as of the data lock point.[1] Because of the larger number of reports in the Applicant's database compared to our search of VigiBase, and the ability to review narratives in cases provided by the Applicant, DPV requested that DDD submit an information request to the Applicant for their postmarketing safety reports.

DPV also requested that the Applicant submit the four PSRs before the one submitted with the BLA for our review.

1.1.2 Endotoxemia

Bacterial endotoxins are lipopolysaccharides found in the outer membrane of gram-negative bacteria.[5] Endotoxins are released upon cell death and lysis and have the potential to contaminate drug and biological products. Depending on the amount of exposure, endotoxins can cause fever, severe inflammatory responses, septic shock, and death.[5] Endotoxin-induced injury may result not from the direct effects of endotoxin itself, but from the production of secondary mediators capable of initiating organ damage and from a cascade of inflammatory responses that can affect nearly all organ systems.[6] Human challenge studies with reference standard endotoxin have been used to study the pathways initiated in infections. Typically, within 50-90 minutes of reference standard endotoxin infusion, flu-like symptoms begin that resolve within three to four hours.[7] Fever, the hallmark of endotoxin infusion, usually develops after a latent period of up to 2 hours, peaks at 1-2 degrees Celsius (°C) above baseline, and can last up to 3-4 hours, depending on the dose.[7] The inflammatory response triggered by endotoxin depends on both the dose and the route of administration.[8] Table 1 includes examples of target organ responses observed following intravenous endotoxin challenge at low and high dose.[8]

Table 1. Select Examples of Target Organ Responses Following Intravenous Endotoxin Challenge

Endpoints Evaluated	Low-Dose (0.06-0.08 ng/kg)	High-Dose (1-4 ng/kg)
Vital signs	Limited or no changes in heart rate, blood pressure, temperature	Fever, increased heart and respiratory rates, hypotension
Constitutional Symptoms		Chills, rigors, malaise, myalgia, headache, nausea
Central nervous system	Altered memory, depressed mood, anhedonia, anxiety, altered cognitive performance	Changes in sleep, reduced cerebral blood flow
Blood cytokines	Increase in TNF, IL-6, IL-10, IL-1 receptor antagonist	Increase in multiple cytokines and chemokines, including TNF and IL-6
Endocrine	Variable increase in cortisol, norepinephrine	Increased adrenocorticotropic hormone, cortisol, growth hormone, procalcitonin, ghrelin, epinephrine
Hematologic	Increased neutrophils, decreased lymphocytes	Increased leukocytes, monocytopenia, decreased lymphocytes with shift toward T-helper 2 cytokine response, enhanced fibrinolysis, activation of coagulation pathways

Table 1. Select Examples of Target Organ Responses Following Intravenous Endotoxin Challenge		
Endpoints Evaluated	**Low-Dose (0.06-0.08 ng/kg)**	**High-Dose (1-4 ng/kg)**
Cardiovascular		Increased cardiac output, decreased LV function, decreased mean arterial pressure
Respiratory		Increased respiratory frequency, decreased inspiratory time, widened alveolar-arterial oxygen tension gradient, dyspnea
IL-interleukin, LV-left ventricular, TNF-tumor necrosis factor		

1.2 REGULATORY HISTORY

MediWound, Ltd. submitted Investigational New Drug application (IND) 065448 for Debridase on July 30, 2002. On August 20, 2003, FDA granted Debrase orphan drug designation for the debridement of acute, deep dermal burns in hospitalized patients.

The Applicant submitted BLA 761192 for NexoBrid on June 29, 2020. They requested (b) (4) [redacted]

1.3 RELEVANT PRODUCT LABELING

The Applicant's proposed labeling for NexoBrid potentially relevant to endotoxemia or adverse events discussed in this review includes the following:[10]

(b) (4) [redacted]

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(b) (4)

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

We included all postmarketing ICSRs submitted by the Applicant for NexoBrid.[11]

We included FAERS cases, literature case reports, and other publications reporting adverse events suggestive of endotoxemia (see Table 1) or other adverse events relevant to the NexoBrid labeling with the use of concentrate of proteolytic enzymes enriched in bromelain, Debrase, Debridase, Debriding Gel Dressing, DGD, EscharEx, or NexoBrid.

We excluded cases reporting:

- Use of unspecified bromelain-containing topical products
- Use of other topical enzymatic debridement products, such as Debridace, a product containing papain and urea[12]
- Use of bromelain by routes other than topical or by unspecified routes

2.2 VIGIBASE SEARCH STRATEGY

DPV searched the VigiBase database with the strategy described in Table 2. VigiBase is a global database of more than 20,000,000 ICSRs maintained by the World Health Organization-Uppsala Monitoring Centre. VigiBase includes ICSRs from 1968 on and from more than 130 countries.[13] DPV has access to VigiBase, and can retrieve information, such as the number of ICSRs for a product, the countries the reports originate from, Preferred Terms (PTs) coded for the ICSRs, and case characteristics. Case narratives, however, are not available in VigiBase. Some pharmacovigilance centers may provide complete ICSRs, including case narratives, on request.

Table 2. VigiBase Search Strategy*	
Date of search	September 23, 2020
Time period of search	Through September 21, 2020
Search type	VigiLyze
Product terms	Trade Name: Debrase, Debridase, Debriding Gel Dressing, DGD, EscharEx, NexoBrid
MedDRA search terms (Version 23.0)	All adverse events
* See Appendix A for a description of the VigiBase database MedDRA-Medical Dictionary for Regulatory Activities	

2.3 POSTMARKETING INDIVIDUAL CASE SAFETY REPORTS SUBMITTED BY APPLICANT

DPV reviewed the 177 ICSRs submitted by the Applicant on October 19, 2020.[11]

2.4 LITERATURE SEARCH

DPV searched the medical literature with the strategies described in Table 3 to identify cases or other publications reporting events suggestive of endotoxemia or other adverse events with NexoBrid use potentially relevant to the NexoBrid labeling.

Table 3. Literature Search Strategy	
Date of search	October 9, 2020
Database	Embase, PubMed
Search terms	**Embase Search #1:** (bromelain OR Debrase OR Debridase OR Debriding Gel Dressing OR EscharEx OR NexoBrid) AND (blood clotting disorder OR endotoxemia OR endotoxic shock OR endotoxin OR fever OR hypotension OR multiple organ failure OR sepsis OR septic shock **Embase Search #2:** (bromelain OR Debrase OR Debridase OR Debriding Gel Dressing OR EscharEx OR NexoBrid); filters applied for Adverse drug reaction, Complication, Drug toxicity, or Side effect **PubMed:** (bromelain OR Debrase OR Debridase OR Debriding Gel Dressing OR EscharEx OR NexoBrid) AND (adverse drug reaction OR blood coagulation disorder OR endotoxemia OR endotoxic shock OR endotoxin OR fever OR hypotension OR multiple organ dysfunction syndrome OR sepsis OR septic shock
Years included in search	All
Limits	English

2.5 PERIODIC SAFETY REPORTS

DPV screened the following PSRs for the Applicant's assessment of safety signals or cases relevant to endotoxemia or to other serious adverse reactions with NexoBrid use:

- PBRER covering December 18, 2018 to December 17, 2019[1]
- PBRER covering December 18, 2017 to December 17, 2018[14]
- Periodic Safety Update Report (PSUR) covering December 18, 2016 to December 17, 2017[15]
- PSUR covering December 18, 2015 to December 17, 2016[16]
- PSUR covering December 18, 2014 to December 17, 2015[17]

2.6 EUROPEAN MEDICINES AGENCY

DPV requested information via e-mail from the EMA on October 8, 2020 regarding safety signals currently under evaluation or being monitored for NexoBrid.

2.7 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 4 for reports relevant to this review as FAERS may include reports for products approved outside of the United States.

Table 4. FAERS Search Strategy*	
Date of search	September 22, 2020
Time period of search	Through September 21, 2020
Search type	FDA Business Intelligence Solution Quick Query
Product terms	Product Name: Debrase, Debridase, Debriding Gel Dressing, DGD, EscharEx, NexoBrid Product Active Ingredient: .Alpha.Amylase (Aspergillus oryzae)\Bromelains\Chymotrypsin\Lysozyme\Pancrelipase\Pancrelipase lipase\Papain\Trypsin, Betaine\Bromelains\Cellulase\Pancrelipase\Papain, Bromelains, Bromelains\Chymotrypsin\Lipase\Pancrelipase\Pancrelipase Amylase\Papain\Rutin\Trypsin, Bromelains\Trypsin, Stem bromelain
MedDRA search terms (Version 23.0)	All adverse events
* See Appendix B for a description of the FAERS database. MedDRA-Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 VIGIBASE

The VigiBase search retrieved 34 reports. See Table 5 for the distribution of reports by country. None of the cases were coded with the PTs *Endotoxaemia* or *Endotoxic shock*. Because case narratives are not available in VigiBase, DPV chose to request the ICSRs from the Applicant in lieu of requesting the narratives for these 34 ICSRs from the submitting pharmacovigilance centers.

Table 5. VigiBase Report Count by Country for NexoBrid (N=34)	
Country	**Number of ICSRs**
United Kingdom	10
Germany	5
Spain	5
Italy	4
Netherlands	2
Poland	2

Table 5. VigiBase Report Count by Country for NexoBrid (N=34)	
Country	**Number of ICSRs**
Romania	2
Sweden	2
Finland	1
Slovakia	1
ICSRs-Individual Case Safety Reports	

3.2 POSTMARKETING INDIVIDUAL CASE SAFETY REPORTS SUBMITTED BY APPLICANT

Table 6 summarizes the 177 ICSRs reported with NexoBrid for this case series. The Applicant's submission of the ICSRs includes a line listing.[11]

Table 6. Descriptive Characteristics of Postmarketing Reports with NexoBrid, Submitted to the FDA by the Applicant on October 19, 2020 (N=177)		
Year received by Applicant	2015	12
	2016	17
	2017	30
	2018	23
	2019	68
	2020	27
Coded outcomes*	Death	12
	Disability	1
	Hospitalization	6
	Life-threatening	4
	Other serious	18
	Non-serious	147
Country	Austria	2
	Belgium	12
	Finland	1
	Germany	31
	Israel	7
	Italy	35
	Korea (North)	1
	Korea (South)	6
	Netherlands	3
	Romania	8
	Slovakia	2
	Spain	44
	Sweden	2
	Switzerland	2
	United Kingdom	21

Table 6. Descriptive Characteristics of Postmarketing Reports with NexoBrid, Submitted to the FDA by the Applicant on October 19, 2020 (N=177)		
Report source† (n=176)	Healthcare provider	176
	Medical literature	121
Age, years (n=118)	<18	31
	18 to 65	72
	>65	15
Sex (n=117)	Female	38
	Male	79
Indication for use† (n=172)	Burn, chemical	14
	Burn, electrical	7
	Burn, thermal	90
	Burn, not specified	54
	Chronic ulcer	13
Total NexoBrid dose, grams‡ (n=59)	≤5	22
	>5 to 10	11
	>10 to 15	6
	>15 to 20	2
	>20 to 25	7
	>25 to 30	4
	>30	7
Total body surface area of NexoBrid application, percent‡ (n=115)	≤15	73
	>15 to 30	22
	>30 to 45	12
	>45	8
Area(s) of NexoBrid application† (n=108)	Abdomen/trunk	35
	Extremities	69
	Face/head/scalp	25
	Hands/feet/digits	46
	Genital/perianal	3
Report type	Spontaneous	177

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.
† Some cases reported more than one
‡ Some cases received multiple treatment sessions

Table 7 lists the Medical Dictionary for Regulatory Activities (MedDRA) PTs reported in the ICSRs. No ICSRs were coded with the PTs *Endotoxaemia* or *Endotoxic shock*.

Table 7. Reported MedDRA Preferred Terms with NexoBrid, Sorted by Decreasing Number of Reports Per Preferred Term* (N=177)		
Preferred Term	**Reports**	**Notes**
Off label use	122	See Section 3.2.1
Pain	26	
Sepsis	6	See Section 3.2.3

Table 7. Reported MedDRA Preferred Terms with NexoBrid, Sorted by Decreasing Number of Reports Per Preferred Term* (N=177)		
Preferred Term	**Reports**	**Notes**
Therapeutic product effect incomplete	6	
Wound complication	6	
Drug ineffective	5	
Haemorrhage	5	See Section 3.2.5
Multiple organ dysfunction syndrome	5	See Section 3.2.4
Wound infection	4	
Acute kidney injury	3	Cases discussed in Section 3.2.4
Cardiac disorder	3	Cases discussed in Section 3.2.4
Hypotension	3	Two cases discussed in Sections 3.2.5 and 3.2.6; third case from an abstract with no case-level information[18]
Respiratory disorder	3	Cases discussed in Section 3.2.4
Thermal burn	3	
Anaphylactic reaction	2	See Section 3.2.6
Cardiac arrest	2	Cases discussed in Section 3.2.5
Excessive granulation tissue	2	
Hyperkalaemia	2	
Impaired healing	2	
Pneumonia	2	Cases discussed in Section 3.2.4
Pyrexia	2	See Section 3.2.2
Abdominal compartment syndrome	1	Case discussed in Section 3.2.5
Acute respiratory failure	1	Case discussed in Section 3.2.6
Anaemia	1	See Section 3.2.5
Anaphylactic shock	1	See Section 3.2.6
Bacteraemia	1	
Blood pressure decreased	1	Case discussed in Section 3.2.5
Blood pressure immeasurable	1	Case discussed in Section 3.2.5
Body temperature increased	1	See Section 3.2.2
Cardiac failure	1	Case discussed in Section 3.2.6
Cardiovascular disorder	1	Case discussed in Section 3.2.6
Cerebral infarction	1	Case discussed in Section 3.2.5
Chemical burn	1	
Circulatory collapse	1	Case discussed in Section 3.2.5
Coagulation test abnormal	1	Case discussed in Section 3.2.2
Cold sweat	1	Case discussed in Section 3.2.5
Dermal cyst	1	
Diabetes mellitus inadequate control	1	
Drug interaction	1	
Dyspnoea	1	Case reported “difficult anatomic airway” not related to NexoBrid use
Electrocardiogram QRS complex abnormal	1	Case discussed in Section 3.2.6

Table 7. Reported MedDRA Preferred Terms with NexoBrid, Sorted by Decreasing Number of Reports Per Preferred Term* (N=177)		
Preferred Term	**Reports**	**Notes**
Erythema	1	
Headache	1	Case discussed in Section 3.2.2
Hemiparesis	1	Case discussed in Section 3.2.5
Hyperaesthesia	1	
Hypertension	1	
Hyperthermia	1	Case discussed in Section 3.2.2
Infection	1	
Inflammatory marker increased	1	Case discussed in Section 3.2.2
Malaise	1	Case discussed in Section 3.2.5
Maternal exposure during breast feeding	1	
Medication error	1	
Metabolic acidosis	1	Case discussed in Section 3.2.6
Muscle twitching	1	
Nightmare	1	
Ocular hyperaemia	1	Case discussed in Section 3.2.2
Pallor	1	Case discussed in Section 3.2.5
Platelet count decreased	1	Case discussed in Section 3.2.5
Pruritus	1	Case discussed in Section 3.2.6
Pulseless electrical activity	1	Case discussed in Section 3.2.5
Rash	1	Case discussed in Section 3.2.6
Renal failure	1	Case discussed in Section 3.2.5
Respiratory failure	1	Case discussed in Section 3.2.5
Septic shock	1	See Section 3.2.3
Shock	1	Case discussed in Section 3.2.4
Skin graft scar contracture	1	
Skin irritation	1	
Supraventricular tachycardia	1	Case discussed in Section 3.2.6
Tachycardia	1	Case discussed in Section 3.2.6
Tachypnoea	1	Case discussed in Section 3.2.2
Therapeutic response decreased	1	
Toxicity to various agents	1	Case discussed in Section 3.2.5
Treatment failure	1	
Underdose	1	
Urticaria	1	Case discussed in Section 3.2.6
Venous haemorrhage	1	See Section 3.2.5
* A report can include more than one MedDRA Preferred Term. MedDRA-Medical Dictionary for Regulatory Activities		

Except for the category of off label use, cases that reported multiple events are included in only one section below, with the category based primarily on the PTs coded in the cases. In cases coded with multiple PTs, we selected the category based on the seriousness of the events or the

events with the strongest temporal relationship to NexoBrid use. The categories below represent the most frequently reported PTs (*Off label use*), events potentially related to or suggestive of endotoxemia (fever, sepsis, multiple organ dysfunction syndrome [MODS], coagulation disorders), or other serious adverse events relevant to the Applicant's proposed labeling (anaphylaxis). Units for diagnostic assessments are included if they were included in the report.

3.2.1 Off label use

As seen in Table 7, *Off label use* was the most frequently reported PT in the cases. Some of the cases coded with the PT *Off label use* reported use that is not off label based on the Applicant's proposed labeling. This includes use on >15% to (b)(4)% total body surface area (TBSA) and administration of NexoBrid as two applications at different times. As seen in Table 6, off label use was reported in pediatric patients, use for treatment of chronic ulcers, electrical or chemical burns, and use on > (b)(4)% TBSA. Other off label use included use in a patient who was breastfeeding and removal of NexoBrid before or after the recommended four hours.

The majority of cases did not specify if NexoBrid was administered in one or more applications. Twenty-one cases reported more than one application of NexoBrid. The number of applications reported in these 21 cases was: two (18), three (1), four (1), and unspecified multiple (1).

3.2.2 Fever

Four cases were coded with PTs related to fever (*Pyrexia, Body temperature increased,* and *Hyperthermia*). A case reporting fever the day of NexoBrid use but not coded with a fever-related PT is included in Section 3.2.6 (MEDI0000129).

A 46-year-old man whose lower legs were burned following exposure to cement experienced fever and other adverse events, including hypotension, three hours after NexoBrid application (MEDI0000050). The patient had no other comorbidities. Three days after the injury, NexoBrid was applied to 14% TBSA. Three hours after application, the patient experienced a temperature of 38.5°C, pain, difficulty breathing, headache, and red conjunctiva. White blood cell (WBC) count was 12,700 (differential not provided), blood pressure (BP) was 80/50, partial pressure of oxygen (pO_2) was 88% on room air, hemoglobin was 19.3, and chest radiograph was normal. NexoBrid was removed, and he was treated with antibiotics and oxygen via mask. Blood cultures were negative. His symptoms resolved within one hour.

A 41-year-old man who sustained second-degree burns to 15% TBSA following an industrial aerosol explosion experienced fever and coagulation abnormalities after treatment with NexoBrid (MEDI0000190). This case was published in the medical literature.[19] The patient had a history of tobacco, cannabis, alcohol, and occasional cocaine use. He was intubated and fluid resuscitated prior to NexoBrid use. One day after admission, NexoBrid was applied to 6% TBSA. Concomitant medications included unspecified sedatives and analgesics. After four hours, NexoBrid was removed, and two hours later the patient's temperature was 40°C "without hemodynamic instability." The case did not report the patient's other vital signs. After cultures were taken, antibiotics were started. Twenty-four hours after debridement, the patient, whose coagulation parameters were previously normal, had a prothrombin time ratio of 1.78 and an activated partial thromboplastin time (aPTT) ratio of 1.24. Platelet count was 110,000 $x10^6$/L and hemoglobin was 9.8 g/dL. Coagulation parameters normalized 24 hours after administration of

intravenous vitamin K. The patient later developed tracheobronchitis and a central line infection, both of which improved with antibiotics. The patient recovered and was discharged. The authors attributed both the hyperthermia and coagulation abnormalities to NexoBrid.

A 42-year-old man who received two applications of NexoBrid 48 hours apart developed a temperature of 38.5°C (MEDI0000185).[20] The case, from a foreign language publication, provides limited information and does not specify when the fever developed in relation to either of the NexoBrid treatments.

Finally, a case from a published abstract reported that an unspecified number out of eight patients treated with NexoBrid experienced "temporary fever or elevated inflammation parameters…shortly after debridement…disappearing completely after a couple of days with no clinical correlation (MEDI0000106)."[21]

Reviewer's comment: The first two cases reported a temporal association between fever and NexoBrid use. The first case reported other signs and symptoms, including headache and hypotension, that could potentially be consistent with endotoxin exposure. The second case reported coagulation abnormalities, which can also be observed with endotoxin exposure, although it is difficult to determine the contribution of NexoBrid to the coagulation abnormalities because they occurred a day after NexoBrid use. Factors other than NexoBrid, such as infection, burn-induced coagulopathy, and possibly hypersensitivity in the first case could also have contributed. The remaining cases did not provide sufficient information to assess the role of NexoBrid.

3.2.3 Sepsis and septic shock

Six cases were coded with the PT *Sepsis* and one case was coded with the PT *Septic shock*. None of the cases reported cultures or bacteremia.

One case reported sepsis and MODS in a 29-year-old man seven days after treatment with NexoBrid, and approximately 19 days after sustaining burns to 53% TBSA (MEDI0000439). The case provided limited information on the patient's clinical course.

The five other cases reporting sepsis were from a published abstract describing experience with NexoBrid in "over 50" cases (MEDI0000388, MEDI0000420, MEDI0000421, MEDI0000422, MEDI0000430).[22] The abstract did not provide case-level data. Although the Applicant contacted the authors for additional follow-up, the information they obtained was limited. Three of the five cases reported the time to onset of sepsis relative to NexoBrid use, which ranged from 5 to 78 days after application (or after the last application if NexoBrid was applied more than once).

A 62-year-old man experienced septic shock and died eight days after being treated with NexoBrid (MEDI0000455). He sustained burns to 76% TBSA following a gas explosion. His medical history was non-contributory, and the report did not provide concomitant medications. Eleven days after the injury, the patient was treated with NexoBrid 20 g to an area of less than 15% TBSA. Eight days later, the patient experienced septic shock and died the same day.

Reviewer's comment: The clinical presentation of sepsis and septic shock are similar to endotoxemia and endotoxemic shock. There was not a strong temporal relationship between the onset of symptoms of sepsis or septic shock and NexoBrid use in the cases that reported time to onset to suggest that the events were related to NexoBrid use.

3.2.4 Multiple Organ Dysfunction Syndrome

Five cases were coded with the PT *Multiple organ dysfunction syndrome*. One of these cases also reported sepsis and is included in Section 3.2.3 (MEDI0000439).

A 57-year-old man experienced burn shock, MODS, and died one day after NexoBrid use (MEDI0000438). He experienced chemical burns to 85% TBSA after falling into an ammonia storage tank. Three days after the injury, NexoBrid was applied to 10% TBSA. The patient experienced "lung haziness " on chest radiograph and acute kidney injury an unspecified time relative to NexoBrid use. The day after NexoBrid use, the patient died due to MODS. The case did not provide information on the patient's laboratory values or clinical status at the time of NexoBrid use.

The remaining three cases reporting MODS were from a published abstract evaluating NexoBrid use in 30 patients that did not provide case-level data (MEDI0000442, MEDI0000443, and MEDI0000444).[23] The Applicant obtained limited follow-up, but the cases did not report the time from NexoBrid application to MODS. The three patients died, but the reporter did not attribute the events in the cases, which also included acute kidney injury and pneumonia, to NexoBrid use.

Reviewer's comment: The information provided in the cases was insufficient to determine if NexoBrid contributed to MODS or death. MODS can be seen in the setting of infection, for example in sepsis or septic shock, or with non-infectious conditions, such as systemic inflammatory response syndrome (SIRS) with pancreatitis.[24]

3.2.5 Bleeding or coagulation abnormalities

Seven cases were coded with PTs related to bleeding or potential coagulation abnormalities, including *Haemorrhage*, *Venous haemorrhage*, and *Anaemia*. An additional case coded only with the PT *Off label use* is included in this section because it reported coagulopathy (MEDI0000095). Another case reporting a fever followed by a coagulation abnormality is included in Section 3.2.2.

A 43-year-old man experienced bleeding from escharotomy sites, decreased hemoglobin, and hypotension following NexoBrid application; he subsequently died after a complicated clinical course (MEDI0000180). The patient had a history of hepatitis C and suffered mostly full thickness burns to 40% TBSA. His multiple concomitant medications included dalteparin. Prior to NexoBrid application, the patient underwent escharotomies to both upper extremities and the frontal torso. Three hours after application of NexoBrid 25 g to the arms and hands, the patient experienced hypotension, decreased hemoglobin, and a "large amount" of bleeding from "both arms/escharotomies." The patient was treated with diathermy and blood transfusions, but he developed hyperkalemia and subsequent cardiac arrest. He was resuscitated, but his clinical

course was complicated by rhabdomyolysis, renal failure, abdominal compartment syndrome, and respiratory failure. The patient died.

A 37-year-old man developed bleeding from surgical escharotomies, hypotension, and tachycardia after application of NexoBrid (MEDI0000182). His multiple concomitant medications included nadroparin. Two days prior to NexoBrid use, he underwent escharotomies to the arms, wrists, and fingers. The patient experienced heavy bleeding during the NexoBrid application and after its removal, and the areas were sutured. The escharotomy incisions were not protected from the NexoBrid. The patient's heart rate was 100 beats per minute (BPM) and BP was 90/40. The patient was treated with fluid. His hemoglobin dropped to 8.5, platelet count was 95, and International Normalized Ratio (INR) was 1.5. The next day, after additional excision, his hemoglobin dropped to 6.2 and he received packed cells. The patient recovered.

A 61-year-old man experienced two bleeding episodes, one of which resulted in circulatory collapse requiring resuscitation, after NexoBrid use (MEDI0000274). He suffered a burn to 2% TBSA when the dressing of his venous leg ulcer caught fire. His medical history included recurrent deep venous thrombosis (DVT), alcohol abuse, and depression. Concomitant medications included rivaroxaban, mirtazapine, chlordiazepoxide, and multivitamins. One day after the burn and 18 hours after his last dose of rivaroxaban, he was treated with 2 g NexoBrid. Approximately one hour later, he started bleeding from the site. The blood loss was assessed as approximately 2 L. His BP dropped to 58/40, heart rate was 66, and respiratory rate was 17. His BP continued to drop and was unrecordable at times. He stabilized with administration of tranexamic acid, fluids, and red blood cell transfusions. The next day the wound started oozing again, and the patient refused surgical ligation. After walking to the toilet, he was found collapsed in a pool of blood. Cardiopulmonary resuscitation was started, and he received multiple doses of epinephrine for pulseless electrical activity. He was eventually resuscitated and intubated, and he underwent surgical repair of the bleeding vessel. He received multiple units of fresh frozen plasma. His platelet count was low (not specified). Subsequently he experienced left sided weakness and computed tomography showed right posterior cerebral artery infarct. The patient was recovering at the time of the report.

An 83-year-old woman taking rivaroxaban for atrial fibrillation developed bleeding and hypotension following NexoBrid application to a deep thermal burn (MEDI0000161). The patient's medical history also included diabetes and hypertension, for which she took several other concomitant medications. Her prothrombin time was 17.2, and her INR was 1.5. NexoBrid 5 g was applied to 6% TBSA. After one hour, the wound area was bloody, and the patient's blood pressure decreased (not specified). NexoBrid was immediately removed, and her condition stabilized one hour later with the administration of fluids.

A patient of unspecified age ("elderly") and sex experienced two episodes of bleeding after receiving NexoBrid (MEDI0000195). The case did not report medical history or concomitant medication use. NexoBrid was applied 72 hours post-escharotomy. Bleeding was noted one-half hour after NexoBrid application and after NexoBrid removal. The reporter suspected that the escharotomy wound bed was not adequately protected from the NexoBrid. The patient was treated with hemostatic suturing, but later died. The reporter assessed the death as not related to the NexoBrid or the bleeding episodes.

A 61-year-old man experienced small areas of punctuate bleeding following three applications of NexoBrid to a total of 54% TBSA (MEDI0000219).[25] The patient suffered wounds to 95% TBSA and inhalation trauma following an explosion. He had a history of smoking and myocardial infarction. Because the patient was too unstable for surgery, he was treated with NexoBrid to 54% TBSA divided in three applications of 20% TBSA or less. Despite the successful debridement with only small areas of punctuate bleeding noted, the patient died the day of the third NexoBrid application due to acute lung and heart failure.

A 54-year-old man treated with NexoBrid for an electrical burn died due to acute liver failure with severe coagulopathy five days after admission (MEDI00000095). This case was included in a foreign language publication of a descriptive study of NexoBrid use and provide limited information on the case.[26]

A one-year-old boy developed decreased hemoglobin, anemia, and was diagnosed with stress ulcers after treatment with NexoBrid (MEDI0000257). The patient's hemoglobin dropped from 11.2 mg% on the day of admission to 9.5 mg% the next day. NexoBrid was applied the day after admission (dose, application area, and time relative to the hemoglobin of 9.5 mg% not specified). No bleeding at the application area was noted. The following day, the patient's hemoglobin dropped to 4.3 and "coffee ground" was observed. Enteral feedings were changed to parenteral nutrition and ranitidine was started. The hemoglobin improved following transfusion, but melena appeared when enteral nutrition was restarted, and hemoglobin decreased again. Gastroscopy showed stress ulcers. Pantoprazole was started, and the patient recovered.

Reviewer's comment: Bleeding at the treatment area or at escharotomy sites was reported in six patients temporally related to NexoBrid use. Four of these patients were receiving concomitant anticoagulants. The case reporting coagulopathy and acute liver failure provided limited information. In the pediatric patient with stress ulcers, the patient's hemoglobin may have started to decrease prior to the use of NexoBrid, making it difficult to determine the contribution of NexoBrid. Although endotoxin-induced coagulopathy related to NexoBrid use is one potential cause, the enzymatic debriding action of NexoBrid and burn-induced coagulopathies are other possible contributory factors.

3.2.6 Anaphylaxis and anaphylactic shock

Three cases, including one case reporting death, were coded with the PTs *Anaphylactic reaction* or *Anaphylactic shock.* An additional case coded with the PT *Urticaria* is included in this section because it was initially categorized as "possibly anaphylaxis" and is relevant to hypersensitivity.

A 40-year-old man became "unstable" 2 hours after removal of a second application of NexoBrid and subsequently died (MEDI0000436). The autopsy report listed the cause of death as "ostensible allergic reaction." The patient sustained burns to 14% TBSA, including circular burns around the neck, following consecutive explosions. Medical history was not provided. He was intubated and in an induced coma. He received multiple concomitant medications, including flucloxacillin for methicillin-sensitive *Staphylococcus aureus* in tracheal secretions, ophthalmic ofloxacin, enoxaparin, and ipratropium and salbutamol for bronchospasm during ventilation. Two days post-burn he was treated with 5 g NexoBrid to 2.5% TBSA on the hands. Two days

later, he was treated with 2 g NexoBrid to 1% TBSA on the neck. Two hours after the NexoBrid was removed, the patient's oxygen saturation decreased, and he was treated with rocuronium for "more invasive ventilation." The patient developed supraventricular tachyarrhythmias, polymorphic ventricular QRS complexes, and ST segment elevations in multiple leads. Transthoracic echocardiogram showed apical and septal hypokinesia. The case does not describe skin or mucosal symptoms or report BP or temperature. Coronary angiography was negative, and ventricular tachycardia improved with amiodarone. The patient was treated with prednisolone, antihistamines, and epinephrine for suspicion of a hyperdynamic allergic reaction to NexoBrid. The patient also received fluids, norepinephrine, dobutamine, glucose, and insulin, but asystole occurred, requiring resuscitation. The patient's potassium was 7.1 mmol/L and dialysis was initiated. The patient continued to be unstable and died due to cardiovascular failure. Autopsy results showed cyanosis of the mucosa, erythema of the respiratory mucosa, acute central nervous system death with swelling of the brain, and hyperhydration of the lungs. Tryptase was 6.63 uL/L (reported as within the normal range of <11.40 uL/L) and immunoglobulin E was 239 kU/L (normal reported as 1-100 kU/L). Multiple drugs, primarily those administered while an inpatient, were detected in venous blood. Additional autopsy results showed acute blood congestion of the lungs and pneumonia. No degranulated mast cells were visible on histologic staining. The cause of death on the autopsy report, which was initially described as "most likely allergic shock" was changed to "ostensible allergic reaction."

A 64-year-old man experienced anaphylaxis with an elevated tryptase level shortly after the application of NexoBrid (MEDI0000129). He was treated with NexoBrid 48 hours after sustaining flash flame burns to an arm and both legs (the case reported conflicting information on TBSA involvement). He was a non-smoker and non-drinker with no allergies. He reported never eating pineapple previously. His multiple concomitant medications included oral bromelains (for pain and started the day before NexoBrid application), topical chlorhexidine, lorazepam, gabapentin, morphine, dihydrocodeine, ketamine, fentanyl, alfentanil, and dalteparin (time relative to administering NexoBrid not provided). NexoBrid (conflicting information on dose) was applied two days after the injury and 30 minutes after receiving an unspecified oral sedative. Five to 10 minutes after the application of NexoBrid was complete, the patient complained of severe pain, and became hypotensive (BP 90/60 mm Hg), tachycardic, febrile, and developed erythema of the face, torso, and legs. He was treated with hydrocortisone and chlorpheniramine and was transferred to the operating room (OR) for removal of NexoBrid under general anesthesia. Tryptase was 21.20 ng/mL (normal range not reported, but usually ranges from 1 to 11 ng/mL), and the highest temperature that day was 38.4°C. [27] He required unspecified vasoconstrictors and was intubated. After NexoBrid removal, the erythema and fever resolved. The following day, tryptase was 3.86 ng/mL.

A 64-year-old woman experienced anaphylaxis, hypotension, and rash 10 minutes after application of 5 g NexoBrid to 3% TBSA (MEDI0000184). Information on the patient's medical history and type of burn were not provided. She had no history of allergy to pineapple. Concomitant medications included mepivacaine, ropivacaine, acetaminophen, and metamizole. The case did not describe her symptoms or clinical course or provide BP. She was treated with cafedrine and an antihistamine. Her symptoms resolved following removal of NexoBrid.

Finally, an 18-year-old man developed pruritus, urticaria, and rash that was initially categorized as "possible anaphylaxis" starting approximately one hour after NexoBrid application. Medical history was not provided. Concomitant medications included chlorhexidine, dalteparin, dihydrocodeine, lorazepam, morphine, acetaminophen, and bupivacaine and lidocaine for local anesthesia. Two g of NexoBrid was applied to 2% TBSA on the hand and wrist. Sixty-five minutes later, the patient noted pruritus. Oxygen saturation was 94% (prior oxygen saturation not provided) and heart rate was 100 BPM. He developed hives around the shoulders which spread rapidly over the chest and back, and the patient became "distressed." Nexobrid was removed, and he was treated with chlorpheniramine, intravenous hydrocortisone, and fluids. Respiratory rate was 22. Tryptase was 7.8. Symptoms improved in less than two hours. The next day, tryptase was 2.5. According to the physician, the patient did not experience respiratory compromise, hypotension, or anaphylaxis. The regional allergy unit did not identify etiological factors other than NexoBrid.

Reviewer's comment: The case reporting death and possible anaphylactic shock did not provide information to conclude that the case met the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) symposium criteria for anaphylaxis (the Sampson criteria).[28] However, there was a temporal relationship of the patient's clinical deterioration to receiving his second dose of NexoBrid, and the autopsy did not identify other factors thought to contribute to the events. The second case appeared to meet the NIAID/FAAN criteria and reported an elevated tryptase level. The third case provided limited clinical details of the event. Although the case reporting urticaria did not provide information on the assessment by the "allergy unit" to determine how the causative drug was determined to be NexoBrid, according to the treating physician, the patient did not experience anaphylaxis.

All cases reported a strong temporal relationship of the events to the NexoBrid application. Two cases reported previous exposure to bromelain, one from a previous dose of NexoBrid and one from treatment with oral bromelain. The case reporting oral bromelain use did not report if the patient received oral bromelain following the event. However, the patients were receiving multiple other medications, and the cases did not describe how the burns were prepared for the NexoBrid application (the Applicant's proposed labeling recommends pre-soaking with an antibacterial solution).[10] With the exception of the death case, all cases reported improvement following removal of NexoBrid. The Applicant's proposed labeling includes (b) (4) (b) (4)

3.3 LITERATURE SEARCH

We identified the three publications below that were not included in the postmarketing reports and that are potentially relevant to symptoms observed with endotoxemia or other serious adverse events relevant to the NexoBrid labeling. We did not identify cases or publications reporting endotoxemia.

Rosenberg L, Lapid O, Bogdanov-Berezovksy A, et al. Safety and efficacy of a proteolytic enzyme for enzymatic burn débridement: a preliminary report. Burns. 2004; 30:843-850.[29] This prospective, non-comparative study of Debridase was conducted in burn patients treated from 1984 to 1999. Of the more than 250 consecutive patients that were treated in the study,

"complete records" were available for 130 patients. All adverse events that occurred during hospitalization were reported, and their relationship to Debridase use was based on "their nature and timing in relation to the débridement." Fever was defined as a temperature >38.5°C, and a rise in temperature of greater than 1°C within 48 hours post-debridement was considered as possibly related to the treatment. The most common adverse events that were categorized as possibly related to debridement were fever (33.8%), localized pain (11.5%), sepsis (1.5%), and a localized burning sensation (1.5%). The overall incidence of fever and sepsis were 79.2% and 6.9%, respectively.

Rosenberg L, Krieger Y, Bodganov-Berezovksi, et al. A novel rapid and selective enzymatic debridement agent for burn wound management: A multicenter RCT. Burns. 2014; 40:466-474.[30]

This multicenter, open-label, randomized, controlled clinical trial enrolled 182 subjects between 2006 and 2009. Twenty-six subjects, the first subject treated at each site, received NexoBrid (for training purposes), and the remaining 156 subjects were randomized to NexoBrid or standard of care (SOC). Safety assessment included vital signs and pain scores assessed before and after debridement and at unspecified times during the first week after debridement. Blood, urine, and bacteriological samples were collected before and 24 hours after debridement. Fever, the most frequently reported adverse event reported in both groups, was 20% in NexoBrid-treated subjects versus 19.8% in subjects who received SOC. Pruritus, wound infection, and pain were slightly higher in the SOC group. The time the adverse events were reported relative to the debridement was not specified.

Shoham Y, Krieger Y, Rubin G, et al. Rapid enzymatic burn debridement: A review of the paediatric clinical trial experience. Int Wound J. 2020; 17:1337-1345.[31]

This publication summarizes the pediatric clinical trial experience with NexoBrid. In a randomized, controlled, open-label phase III study comparing NexoBrid to SOC conducted between 2006 and 2009 in 182 subjects (see publication by Rosenberg, et al. above), 17 pediatric subjects (4 to 18 years) were treated with NexoBrid, and 16 pediatric subjects were treated with SOC. Fever was reported in 28.6% of pediatric subjects treated with NexoBrid, versus 31.2% treated with SOC. Sepsis and bacteremia were reported in 7.1% each of NexoBrid-treated subjects (the publication does not specify if they were the same subjects), and bacteremia was reported in 6.3% of pediatric subjects treated with SOC. No cases of sepsis were reported in the pediatric subjects treated with SOC.

Reviewer's comment: The difference in the incidence in fever in NexoBrid-treated subjects in the studies above, ranging from 20 to 33.8%, (b) (4) (b) (4) *We cannot determine if these differences are related to differences in the assessment of fever in subjects in the various studies, changes to the manufacturing process or the formulation of Debridase/NexoBrid, changes in the care of patients with burns over time, or other factors. Although the patient populations differ, the incidence of sepsis reported in the pediatric clinical trial experience of 7.1%* (b) (4) (b) (4)

3.4 PERIODIC SAFETY REPORTS

Information in the PSRs relevant to this review include the Applicant's evaluation of hypersensitivity and anaphylaxis, a case of SIRS in a pediatric clinical trial subject, and drug utilization data.

The Applicant identified hypersensitivity as a new safety signal in the PSR covering December 2015 to December 2016 after identification of cases of suspected anaphylaxis in a 64-year-old man, possible anaphylaxis in an 18-year-old of unspecified sex, and an unspecified allergic reaction in a 25-year-old man.[16] In the next PSR, covering December 2016 to December 2017, the Applicant reported updating their reference safety information, the Summary of Product Characteristics (SmPC), to include serious allergic reactions, including anaphylaxis.[15] The PSR includes a brief analysis of hypersensitivity reactions with NexoBrid use. The Applicant identified five cases of potential hypersensitivity reactions in their safety database using the *Hypersensitivity* Standardised MedDRA Query (broad). One case reported an allergic skin reaction, described as erythema of the face, torso, and feet, in a 25-year-old patient whose BP "continued to fall on administering pain relief." The reaction was treated with removal of NexoBrid and administration of steroids and fluids. The patient's tryptase level was reported as elevated but was not provided. One case in a 48-year-old woman occurred 22 days after NexoBrid application and was attributed to latex allergy. Three remaining cases are summarized in Section 3.2.6. The Applicant's literature search did not identify hypersensitivity reactions to NexoBrid, but identified reports describing sensitization to pineapple and bromelain. According to the PBRER covering December 2017 to December 2018:

> "Two signals (hypersensitivity and anaphylactic reactions) were closed. Warnings about serious allergic reactions including anaphylactic reaction are included in the SmPC of NexoBrid and now represent undesirable effects of the therapy with unknown frequency. As presented above, allergic reactions were re-classified from important potential to identified risk within the EU RMP in updated version 6.1 (dated 15 March 2018). No additional safety-related actions are necessary."[14]

The current SmPC for NexoBrid includes the following information regarding anaphylaxis:[1]

> Hypersensitivity reactions, skin exposure
> There have been reports of serious allergic reactions including anaphylaxis (with manifestations such as rash, erythema, hypotension, tachycardia) in patients undergoing debridement with NexoBrid.
>
> The potential of NexoBrid (a protein product) to cause sensitisation should be taken into account (b) (4) .

The PBRER covering December 2018 to December 2019 includes a description of a case of SIRS temporally related to NexoBrid use from the pediatric study MW2012-01-01 (NCT02278718).[1] While recovering from the anesthesia for the removal of NexoBrid, a 15-month-old girl on multiple concomitant medications developed fever, tachycardia, decreased perfusion, and possible signs of sepsis. Wound and blood cultures were negative, and the wound did not appear infected. She was diagnosed with SIRS. She had a mild rash around the wound,

which worsened the next day, and improved with the application of hydrocortisone cream. The patient had a pre-existing respiratory tract infection and was febrile both before and several times after the NexoBrid application.

According to the PBRER covering December 2018 to December 2019, 874 subjects were enrolled in the clinical development program for NexoBrid through the data lock point of December 17, 2019.[1] These included 534 subjects (61.1%) treated with NexoBrid, 271 subjects (31%) who received SOC, and 69 subjects (7.9%) treated with gel vehicle. The Applicant estimated postmarketing non-clinical trial exposure, based on internal company sales data, at 5,745 subjects worldwide.

Reviewer's comment: The Applicant's (b) (4) *. We did not identify the case of the 25-year-old with a possible hypersensitivity reaction to NexoBrid or the case of the 48-year-old with an allergic reaction attributed to latex in the cases submitted by the Applicant.*

The case of SIRS in the pediatric subject temporally related to NexoBrid use could be suggestive of endotoxemia. However, the patient's underlying respiratory tract infection could have contributed. We did not identify other cases reporting SIRS in the postmarketing reports or the literature.

3.5 EUROPEAN MEDICINES AGENCY

The EMA's response for (b) (5)

(b) (5)

Reviewer's comment: The case reporting fatal anaphylactic shock appears to be case MEDI0000436 in Section 3.2.6. According to the Posology and method of administration section of the SmPC for NexoBrid, "A second and subsequent application is not recommended."

3.6 FAERS

The FAERS search retrieved 67 reports. None of the reports met the case definition in Section 2.1.

4 DISCUSSION

We reviewed 177 foreign postmarketing case reports received by the Applicant from 2015 to 2020. We reviewed the last five PSRs submitted by the Applicant and the published literature relevant to adverse events reported with NexoBrid use and queried the EMA regarding safety signals currently under evaluation. We did not identify relevant cases in FAERS. Although our focus was on events suggestive of endotoxemia based on DDD's request, we also considered other serious adverse events potentially relevant to the NexoBrid labeling.

We did not identify cases or publications reporting endotoxemia, endotoxic shock, or measurement of endotoxin. We grouped the postmarketing cases with symptoms possibly suggestive of endotoxemia into the categories of fever, sepsis, MODS, and coagulation abnormalities. We did not identify postmarketing cases reporting SIRS, but one PSR included a case of SIRS temporally related to NexoBrid in a pediatric clinical trial subject that was confounded by infection.

We identified three cases, including one case reporting anaphylaxis, reporting fever temporally related to NexoBrid use. The onset of fever in these cases is reasonably compatible with the fever seen in experimentally-induced endotoxemia, which can last 3-4 hours after an initial latent period of 1-2 hours.[7] The cases reported other signs, including hypotension, increased WBC count, and coagulation abnormalities, that could be suggestive of endotoxemia. However, these signs are also consistent with the hypermetabolic profile resulting from burn injury.[32] According to the Applicant's proposed labeling, (b) (5) [10] In the publications identified in the literature search in Section 3.3, fever was reported in up to nearly 34% of NexoBrid-treated subjects. The mechanism for NexoBrid to cause fever is unknown.

Cases reporting sepsis and septic shock are also relevant to an assessment of endotoxemia because of the similarity of symptoms. Although none of the seven cases reporting sepsis or septic shock reported culture results or causative organisms, the five cases that reported time to onset did not report a strong temporal association to NexoBrid use. The earliest time to onset was five days after NexoBrid use. During experimentally-induced endotoxemia in humans, cytokine responses peak at 2-3 hours after endotoxin administration and return to baseline values within 6-8 hours.[33] The incidence of sepsis in burn patients ranges from 8-43% and is the leading cause of death.[34]

The cases reporting MODS provided limited information to assess the role of NexoBrid. One case reported the time to onset relative to NexoBrid use. Although the case reported burn shock and MODS the day following NexoBrid application, the patient's extensive chemical burns to 85% TBSA could have contributed. Adults with burns affecting greater than 20% TBSA are at risk of burn shock, and MODS is a major cause of death in burn patients.[34]

We identified eight cases reporting bleeding or abnormalities of coagulation parameters. In some of these cases, factors such as concomitant anticoagulants, possible exposure of escharotomy sites or a chronic venous ulcer to NexoBrid, or both, could have contributed. Some degree of peri-procedural bleeding related to eschar removal, whether by enzymatic or surgical debridement, is expected.[35] In addition, up to 40% of patients with severe burns may experience coagulopathy.[19] Burn care guidelines recommend assessment for risk of DVT, and use of prophylactic anticoagulants, as seen in some of our cases, in patients at high risk of DVT.[36] As described in the Applicant's proposed labeling, (b) (4) (b) (4). Errasti et al. measured the effect of bromelain extract (not NexoBrid) activity on fibrinogen, fibrin, and blood coagulation in vitro, and found that bromelain showed a procoagulant effect at low concentration and an anticoagulant effect at high concentration.[37] Endotoxin has complex effects on coagulation, stimulating both fibrinolysis and local activation of coagulation.[8] Initially, endotoxin activates the fibrinolytic system, with increases in tissue plasminogen activator. However, later increases in plasminogen-activator inhibitor inhibit fibrinolysis.[7] Endotoxin also induces platelet activation and consumption, and can result in a prolonged aPTT and increased INR.[33] There are multiple factors that could have contributed to the bleeding and coagulation disorders in these cases.

Finally, we reviewed three cases coded with PTs related to anaphylaxis and an additional case reporting urticaria with NexoBrid use. In the PSRs, the Applicant concluded that hypersensitivity is an important identified risk, and both anaphylaxis and hypersensitivity related to NexoBrid use are included in the SmPC. The Applicant's proposed labeling includes (b) (4) (b) (4)[10] Although the cases of anaphylaxis reported a strong temporal relationship to NexoBrid use, only one case provided information meeting the NIAID/FAAN criteria (MEDI0000129). The Applicant's assessment of hypersensitivity reactions in the PSR included an additional case that we did not identify reporting skin symptoms, hypotension, and an elevated tryptase. We did not identify cases of anaphylaxis or other serious hypersensitivity reactions in our literature search. According to the response from the EMA to our information request, the EMA is considering further updates to the SmPC for NexoBrid based on the recent death case reporting possible anaphylactic shock (MEDI0000436), with possible consideration for restricting use to one application.

Hypersensitivity reactions to NexoBrid are plausible based on the immunogenicity of the product as described in the ADVERSE REACTIONS section of the proposed labeling. The labeling states that (b) (4) Although we acknowledge that the use of multiple concomitant medications, including pretreatment antibacterial soaks, in the setting of NexoBrid use makes it difficult to determine the causative agent, given the potential for fatal outcomes

with anaphylaxis, labeling for anaphylaxis and urticaria in the setting of NexoBrid use may be warranted.

5 CONCLUSION

We identified a limited number of cases reporting events such as fever, sepsis, MODS, bleeding and coagulation disorders temporally associated with NexoBrid use that could potentially be consistent with endotoxin exposure. Other factors, such as the hypermetabolic state seen in burn patients, burn-induced coagulopathy, infections, and hypersensitivity could also have contributed to the events. We identified cases reporting anaphylaxis with NexoBrid use. Although we cannot rule out the contribution of concomitant medications used around the time of NexoBrid exposure, the Applicant's proposed labeling refers to (b) (4) This is in contrast to the language in the SmPC for NexoBrid.

6 RECOMMENDATIONS

DPV does not have recommendations related to endotoxemia. We recommend consideration of modifying the Applicant's proposed labeling for hypersensitivity to describe the potential for anaphylaxis and (b) (4) with NexoBrid use. Assuming that cases of anaphylaxis and urticaria were not identified in the clinical trials currently under review, we also recommend adding anaphylaxis and urticaria to the *Postmarketing Experience* subsection of ADVERSE REACTIONS. Underlined text is an addition, and strike-through text is a deletion:

> 4 CONTRAINDICATIONS
> (b) (4)
> _exoBrid is contraindicated in patients with a history of hypersensitivity to (b) (4) or any of its excipients, bromelain, pineapple, papaya, or papain.
>
> 5 WARNINGS AND PRECAUTIONS
> *5.7 Hypersensitivity reactions,* (b) (4)
> (b) (4)
> erious hypersensitivity reactions, including anaphylaxis, have been reported with postmarket use of NexoBrid. If a serious hypersensitivity reaction occurs, remove NexoBrid (if applicable) and initiate appropriate therapy.
>
> 6 ADVERSE REACTIONS
> 6.3 *Postmarketing Experience*
> (b) (4)
> he following adverse reactions have been reported during post-approval use of NexoBrid. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ~~drug~~ (b) (4) exposure.
>
> *Immune system disorders:* Hypersensitivity, including anaphylaxis and urticaria

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8 APPENDICES

8.1 APPENDIX A. VIGIBASE DATABASE

VigiBase is a global database of individual case safety reports (ICSRs) received by the Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. VigiLyze is a tool used to search and analyze VigiBase. VigiBase includes ICSRs submitted by over 130 countries, including the U.S., for allopathic medicines, traditional medicines (herbals), and biological medicines, including vaccines. The FDA does not have access to case narratives in VigiBase but may request them from the regulatory authorities that submitted the ICSRs. Some cases in VigiBase may also be in the FDA Adverse Event Reporting System (FAERS). The limitations and qualifications that apply to VigiBase information and its use include:

Tentative and variable nature of the data
Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centers come from both regulated and voluntary sources. Practice varies: some national centers accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centers make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national center until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centers.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

The caveat statement on the cover page of this document must be included in any document or publication that includes VigiBase data

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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