CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	BLA
Application Number	761192
PDUFA Goal Date	January 1, 2023
OSE RCM #	2022-590
Reviewer Name(s)	Timothy Bernheimer, Pharm.D.
Team Leader	Carolyn Tieu, Pharm.D., M.P.H
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 5, 2022
Subject	Evaluation of Need for a REMS
Established Name	Anacaulase-xxxx
Trade Name	NexoBrid
Name of Applicant	MediWound Ltd.
Therapeutic Class	Proteolytic Enzymes
Formulation(s)	Topical gel
Dosing Regimen	Applied topically in up to two applications of 4 hours each. The first application may be applied to an area of up to 15% total body surface area (TBSA). A second application may be applied 24 hours later. The total treatment area for both applications must not exceed 20% TBSA. Dose of 2 grams NexoBrid powder mixed with 20 grams gel per 1% TBSA or 5 grams NexoBrid powder mixed with 50 grams gel per 2.5% TBSA

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity NexoBrid (anacaulase-xxxx) is necessary to ensure the benefits outweigh its risks. MediWound, Ltd. submitted a Biologic Licensing Application (BLA) 761192 for NexoBrid with the proposed indication of treatment for eschar removal in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burn. The risks associated with NexoBrid include hypersensitivity reactions, pain management, proteolytic injury to non-target tissues, and coagulopathy. The applicant did not submit a REMS with this application but proposed a voluntary risk mitigation measure to provide ongoing education of healthcare professionals through publications, speaker programs, grand rounds, education programs, and other information delivered via multiple media at the point of care in the local environment.

DRM has determined that a REMS is not needed to ensure the benefits of NexoBrid outweigh its risks. NexoBrid will likely be prescribed by critical care specialists, intensivists, surgical critical care specialists, and plastic surgeons and/or administered by nurses and/or burn technicians specialized in trauma care in burn centers who have experience in monitoring, diagnosing, and managing the aforementioned risks. These risks will be communicated through labeling.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) NexoBrid (anacaulase-xxxx) is necessary to ensure the benefits outweigh its risks. MediWound, Ltd. submitted a Biologic Licensing Application (BLA) 761192 for NexoBrid with the proposed indication of treatment for eschar removal in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burn. This application is under review in the Division of Dermatology and Dentistry (DDD). The applicant did not submit a proposed REMS with this application.

2. Background

2.1. Product Information

NexoBrid (anacaulase-xxxx), which contains proteolytic enzymes, is a new molecular entity,[a] with the proposed indication of treatment for eschar removal in adults with DPT and/or FT thermal burn. The mechanism of action of action of NexoBrid is to dissolve eschar by enzyme activity, however the specific enzymes responsible for this effect have not been identified. NexoBrid is proposed as lyophilized powder in a gel vehicle mixed as either 2 grams NexoBrid powder with 20 grams gel per 1% total body surface area (TBSA) or 5 grams NexoBrid powder mixed with 50 grams gel per 2.5% TBSA by topical

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

application. The expected duration of treatment is until eschar is dissolved.[b] Due to the severity of burns that require eschar removal, NexoBrid is likely to be administered in intensive care units (ICU), trauma centers, and burn centers. NexoBrid was granted orphan drug designation in 2003. NexoBrid is currently approved in the European Union (December 2012), Argentina (October 2015), Israel (July 2014), South Korea (June 2018), Russia (September 2018), Peru (June 2019), Chile (June 2019), United Kingdom (January 2021), and Switzerland (April 2022).

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761192 relevant to this review:

- 08/20/2003: Orphan drug status granted
- 06/29/2020: BLA 761192 submission for concentrate of proteolytic enzymes enriched in bromelain for treatment of eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns
- 12/14/2020: A post midcycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there are no major safety concerns at this time and there are currently no plans for a REMS.
- 03/24/2021: A late cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant of major chemistry, manufacturing and controls (CMC) and Facility Inspection review issues identified.
- 06/15/2021: Division of Risk Management (DRM) defers comment on the need for a REMS
- 06/25/2021: Complete Response (CR) letter sent to the applicant due to the following deficiencies: multiple outstanding product quality deficiencies, including issues with botanical raw material, drug substance and drug product microbiology; chemistry, manufacturing, and controls; and outstanding facility Inspections.
- 07/01/2022: BLA 761192 resubmission received

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

A burn is an injury to the skin or other organic tissue that occurs when some or all of the cells in the tissue are destroyed, primarily caused by thermal trauma.[1] Thermal burns are injuries caused by flames, hot liquids or hot solid objects. Burn injury interferes with the important functions of intact skin, such as sensation, body temperature regulation, water content regulation and protection against infections, mechanical injury, and radiation present in the environment.[2]

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Estimates derived mainly from federal surveys estimate 486,000 burn injures receiving medical treatment in US annually with 40,000 hospitalizations related to burn injury.[3,c]

Deep partial thickness (DPT) burns involve the epidermis and extend into the dermis. DPT burns cause blistering and healing can only occur once the basal layer of keratinocytes has been restored. Full thickness (FT) burns are injuries that extend through the entire dermis. DPT and FT burn healing is slow, can be complicated by scarring, and treatment by surgical excision is often required.[4] The loss of the intact skin barrier makes these areas more prone to infection, which also prevents healing, endangers the life of the patient and scar formation can cause joint contracture.[5,d] In DPT and FT burns, a waxy eschar develops that prolongs wound healing and some DPT wounds are converted to FT wounds because of infection and desiccation.[7]

3.2. Description of Current Treatment Options

Clinical assessment of burn type and depth determines burn treatment and management options. Partial thickness burns that do not show healing within 1 to 2 weeks may require surgery and patients with deep partial burns have better outcomes with early excision of eschar and grafting.[6] The primary objective of burn wound care is wound closure[7] generally achieved by early surgical excision and eschar removal (debridement) in DPT and FT burn wounds.

Burn eschar removal or debridement is beneficial to wound healing.[8] Currently, the enzymatic debridement agent Collagenase Santyl (collagenase) ointment, approved in 1965, is the only approved product indicated for debriding chronic dermal ulcers and severely burned areas. Collagenase Santyl has the risk of hypersensitivity and the package insert describes the theoretical possibility that debriding enzymes may increase the risk of bacteremia.[9] The Collagenase Santyl label contains no information on the products treatment effect, and the extent of product use in the burn population is unclear.

4. Benefit Assessment

The efficacy of NexoBrid was evaluated from two Phase 3 studies, NCT04040660 or Study 2010-03-02 (2010) and NCT00324311 or Study 2004-11-02 (2004). Study 2010 is the key study supporting efficacy of NexoBrid, while Study 2004 is supportive. The review team notes that Study 2004 was completely open-label and therefore it is difficult to assess the impact of bias.

Study 2010

Study 2010 was a multicenter, randomized, vehicle and standard of care (SOC) controlled, assessor-blinded study to evaluate the efficacy and safety of NexoBrid in subjects with thermal burns. Burns were classified as DPT, FT or superficial partial thickness (SPT). The study periods included an eschar removal

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

stage, a wound closure stage, and a follow-up stage. During the follow-up stage subjects were followed for 24 months to assess wound comesis, function and scarring. Subjects were enrolled under three amendments (amendments 8, 9 and 11) to the protocol and the inclusion criteria and randomization/stratification method differed under the three amendments.

Subjects enrolled under Amendment 8 (21 subjects) and Amendment 9 (32 subjects) were included if they were age 18 to 70, had a total burn area >= 3% DPT and or FT, a total burn area =< 15% TBSA; SPT, DPT and/or FT in depth, or had at least one wound >1% TBSA that was DPT and/or FT but did not include facial, perineal, or genital wounds.

A total of 122 subjects (70%) were enrolled under Amendment 11. The key inclusion criteria differences in amendment 11 is that subjects could have a maximum burn area of 30% TBSA and at least one wound >=0.5%. Subjects were excluded under Amendment 11 if the SPT areas that cannot be demarcated from DPT and FT areas were not less than 50% of the TBSA of the target wound.

Subjects were randomized to NexoBrid gel, SOC, and vehicle gel in a 3:3:1 ratio. NexoBrid or gel vehicle were applied in the same manner (no more than 15%TBSA per treatment session). SOC consisted of the investigator's usual practice using surgical and non-surgical eschar removal procedures. The eschar removal stage was considered complete when >= 95% of eschar was removed.

The baseline demographics were generally balanced across treatment arms. The majority of subjects were male. The majority of subjects were White, followed by Black or African-American, Asian, and other. Fifty-six percent of subjects were enrolled in the Unites States.

The primary efficacy endpoint was the incidence of eschar removal (>=95%) at the end of the topical treatment soaking period for NexoBrid versus gel vehicle. Secondary endpoints included incidence of surgical eschar removal, time to eschar removal, and actual blood loss during the eschar removal procedures. Safety endpoints were comparisons between NexoBrid and SOC and included time to wound closure and Modified Vancouver Scar Scale (MVSS) averaged over target wounds (TWs) at month twelve. MVSS evaluates cosmesis based on pigmentation, pliability, height, vascularity, pain, and pruritus.

For the sensitivity analysis, missing data was treated the least favorable way in that missing data for the NexoBrid arm was treated as not achieving eschar removal, and for the vehicle arm missing data was treated as achieving eschar removal. See Table 1 for study 2010 primary endpoint results.[10]

Table 1 – Incidence of Eschar Removal at the End of the Topical Treatment Period

	NexoBrid N=75	Vehicle N=25	Odds Ratio 95% CI p-value	Risk Difference 95% CI
Primary Analysis[a]	70 (93.3%)	1 (4.0%)	288.28 (35.5, >999.9) <0.001	89.3% (73.6%, 96.2%)
Sensitivity Analysis[b]	70 (93.3%)	2 (8.0%)	141.4 (25.4, 999.8) <0.001	85.3% (68.4%, 94.2%)

Source: FDA BLA Multi-disciplinary Review and Evaluation BLA 761192 for NexoBrid, Table 7. Accessed Oct 24 2022.
[a]Missing data imputed as not achieving eschar removal
[b]Missing data imputed as not achieving eschar removal for the NexoBrid arm and achieving eschar removal on the vehicle arm. Note that all subjects on the NexoBrid arm had observed data.

For the secondary endpoint of incidence of excision for eschar removal, the primary analysis method was logistic regression with terms for treatment, treatment wound depth, total %TBSA per subject and number of treatment wounds. The clinical reviewer also conducted a sensitivity analysis that treats missing data in the least favorable way (missing data are imputed as having an excision for the NexoBrid arm and not having an excision on the SOC arm). See Table 2 for Study 2010 secondary endpoint, Incidence of Excision for Eschar Removal.[10]

Table 2 – Incidence of Excision for Eschar Removal

	NexoBrid N=75	SOC N=25	Odds Ratio 95% CI p-value	Risk Difference 95% CI
Primary Analysis[a]	3 (4.0%)	54 (72.0%)	0.011 (0.003, 0.044) <0.001	-67.4% (-78.2%, -56.6%)
Sensitivity Analysis[b]	3 (4.0%)	48 (64.0%)	0.015 (0.004, 0.060) <0.001	-59.4% (-70.5%, -48.4%)

Source: FDA BLA Multi-disciplinary Review and Evaluation BLA 761192 for NexoBrid, Table 9. Accessed Oct 24 2022.
[a]Missing data imputed as not achieving eschar removal
[b]Missing data imputed as not achieving eschar removal for the NexoBrid arm and achieving eschar removal on the SOC arm. Note that all subjects on the NexoBrid arm had observed data.

The clinical reviewer concludes that NexoBrid was superior to gel vehicle for the primary endpoint, incidence of ≥95% eschar removal, and superior to SOC for the secondary endpoint of incidence of excision for eschar removal.[e]

5. Risk Assessment & Safe-Use Conditions

The clinical development program of NexoBrid consisted of eight studies (six Phase 2 studies and two Phase 3 studies) in which 467 subjects were treated with NexoBrid, 454 of whom were treated at the 2 gram dose proposed in labeling. The two Phase 3 studies formed Cohort 2 and provided the primary safety data. Cohort 2 had 177 subjects enrolled in the NexoBrid treatment group, 149 subjects received SOC, and 24 subjects received gel vehicle.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

There were no treatment emergent adverse events that led to discontinuation of treatment.

There were eight deaths in the clinical program, seven subjects who received NexoBrid and one subject that received study treatment. All of the deaths were considered unrelated to study treatment or there were confounders to the assessment of relatedness (e.g., SOC treatment in same timeframe; underlying illness) by the clinical investigator.

Severe adverse events were slightly higher in the NexoBrid treatment group (9%) compared to the SOC group (7%). In the NexoBrid group there were three (2%) SAEs of pain, three (2%) SAEs of sepsis, and two (1%) SAEs of scar versus two (1%), two (1%), and zero in the SOC group respectively.

The applicant identified pain, pyrexia, wound infection, immediate hypersensitivity reactions, and coagulation parameter abnormalities as key risks of NexoBrid.[f]

The clinical reviewer concludes that the available safety information suggests that the safety profile of NexoBrid in the target population could be similar to SOC.

5.1. Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with postmarketing use of NexoBrid in other countries.

The risk of hypersensitivity reactions will be communicated in the *Warnings and Precautions* section of the labeling. The labeling advises healthcare providers to remove NexoBrid (if applicable) and initiate appropriate therapy if a hypersensitivity reaction occurs. The label also advises that NexoBrid is contraindicated in patients with a known hypersensitivity to anacaulase-xxxx, bromelain, pineapples or to any other component of NexoBrid. NexoBrid is also contraindicated in patients with known hypersensitivity to papayas or papain.

5.2. Pain Management

Severe adverse events of pain were observed in the NexoBrid clinical program. Eschar removal with NexoBrid and treatment-related burn wound procedures are painful. The *Warnings and Precautions* section of labeling will advise healthcare providers that use of NexoBrid and treatment-related burn wound procedures should only be performed under pain management appropriate for an extensive dressing change of burn wounds.

5.3. Proteolytic Injury to Non-Target Tissues

NexoBrid contains proteolytic enzymes and therefore is not recommended for the treatment of burn wounds where medical devices or vital structures could become exposed during eschar removal.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The Warnings and Precautions section of labeling will advise healthcare providers to protect exposed surgical escharotomy sites with skin protectant ointments or ointment gauze to prevent possible exposure to NexoBrid.

5.4. Coagulopathy

Oral administration of bromelain, a component of NexoBrid, has been reported in the literature to possibly cause a reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times. In vitro and animal data suggest that bromelain can also promote fibrinolysis.

The *Warnings and Precautions* section of labeling will advise healthcare providers to avoid use of NexoBrid in patients with uncontrolled disorders of coagulation and caution use in patients on anticoagulant therapy, and in patients with low platelet counts and increased risk of bleeding from other causes. The label advises healthcare providers that patients should be monitored for possible signs of coagulation abnormalities and signs of bleeding.

6. Expected Postmarket Use

Due to the seriousness of DPT and FT thermal burns, it is expected that patients receiving NexoBrid treatment will be hospitalized in ICUs or treated in burn centers. According to the American Burn Association's criteria, patients with partial thickness burns greater than ten percent TBSA and/or any FT burn should be referred to a burn center.[11] Likely prescribers of NexoBrid are critical care specialists, intensivists, surgical critical care specialists, and plastic surgeons who are able to monitor, diagnose, and manage the aforementioned risks. NexoBrid will likely be administered by burn technicians and nurses who specialize in trauma care.

NexoBrid is a topical alternative to surgical removal of burn eschar and is an alternative to the topical Santyl.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for NexoBrid beyond routine pharmacovigilance, labeling and a voluntary risk mitigation measure to provide ongoing education of healthcare professionals through publications, speaker programs, grand rounds, education programs, and other information delivered via multiple media at the point of care in the local environment.

The Applicant states that the "proposed NexoBrid product labeling and other planned elements to ensure safe use described (Health Care Provider Education Program, Planned Educational Brochures for NexoBrid) are adequate to ensure a favorable benefit-risk balance without a formal REMS."

7.1. Other Proposed Risk Management Activities

At this time, two NexoBrid Phase 3 clinical studies (MW2010-03-02 and MW2012-01-01) and 1 expanded access treatment protocol (MW2018-06-21) are ongoing. Each study includes safety surveillance by independent data safety monitoring boards.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of NexoBrid on the basis of the efficacy and safety information currently available.

Typically, the treatment of DPT and FT burns requires excision of the eschar. If left untreated, healing is slow, is complicated by scar formation, and the loss of the intact skin barrier makes the wounds more prone to infection, which endangers the life of the patient. Currently, the only FDA approved treatment for the debridement of burns is Collagenase Santyl which carries the risk of hypersensitivity and may increase the risk of bacteremia.

The serious risks associated with NexoBrid are hypersensitivity reactions, need for pain management, proteolytic injury to non-target tissues, and coagulopathy. The risk of hypersensitivity reactions is shared with the other approved product to treat burns, Collagense Santyl. Collagense Santyl is currently approved without a REMS and the risk of hypersensitivity reactions is communicated through labeling. NexoBrid is a topical alternative to surgical removal of burn eschar. The serious risks of surgical removal of burn eschar are similar to the risks of NexoBrid in that surgical removal of burn eschar shares the need for adequate pain management, and risk of injury to non-target tissue. Clinicians are familiar with the importance of proper pain management because burn treatment guidelines stress the importance of pain management with the treatment of burns.[12] Clinicians that treat burns are familiar with the risk and management of coagulopathy because severe burn injury is associated with systemic coagulopathy.[13] The risks of NexoBrid are similar to the risks of the patient population receiving standard of care for the treatment of burns.[14] As a result, likely prescribers and administrators of NexoBrid are familiar with recognizing and managing the risks of hypersensitivity reactions, need for adequate pain management, proteolytic injury to non-target tissues, and coagulopathy. The aforementioned risks can be mitigated through labeling.

The clinical review team is in agreement and concludes that the Applicant provided substantial evidence of effectiveness and the available safety information suggests that the safety profile of NexoBrid in the target population could be similar to standard of care.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for NexoBrid to ensure the benefits outweigh the risks. In general, healthcare providers who treat DPT and FT burns are familiar with the risk of hypersensitivity reactions, pain management, proteolytic injury to non-target tissues, coagulopathy and the importance of patient monitoring. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

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/s/

TIMOTHY J BERNHEIMER
12/05/2022 09:51:45 AM

CAROLYN N TIEU
12/05/2022 09:53:49 AM

CYNTHIA L LACIVITA
12/05/2022 10:40:17 AM

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

Application Type	BLA
Application Number	761192
PDUFA Goal Date	June 29, 2021
OSE RCM #	2020-1351
Reviewer Name	Yasmeen Abou-Sayed, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	June 15, 2021
Subject	Deferral of Risk Evaluation and Mitigation Strategy (REMS) Review
Established Name	Concentrate of proteolytic enzymes enriched in bromelain gel
Trade Name	NexoBrid
Name of Applicant	MediWound, Ltd.
Therapeutic Class	Proteolytic Enzymes
Formulation	lyophilized powder consisting of a mixture of proteolytic enzymes enriched in bromelain and a gel vehicle used for preparation of a gel for topical use
Dosing Regimen	Applied topically for 4 hours to the burn wound at a dose of 2 g NexoBrid powder mixed with 20 g Gel Vehicle/1% total body surface area (TBSA) or 5 g NexoBrid powder mixed with 50 g Gel Vehicle/2.5% TBSA.

This memorandum documents the deferral of a Risk Evaluation and Mitigation Strategy (REMS) review for Nexobrid (concentrate of proteolytic enzymes enriched in bromelain gel), Biologics License Application (BLA) 761192.

On June 29, 2020, the Division of Dermatology and Dentistry (DDD) requested that the Division of Risk Management (DRM) evaluate the need for a REMS for Nexobrid (concentrate of proteolytic enzymes enriched in bromelain gel) submitted by MediWound, Ltd. with the proposed indication of treatment for eschar removal (debridement) in adults with burn wounds. The submission did not include a REMS.

DDD plans to issue a Complete Response (CR) letter based on the following deficiencies: multiple outstanding Product Quality deficiencies, including issues with Botanical Raw Material, Drug Substance and Drug Product Microbiology; Chemistry, Manufacturing, and Controls; and outstanding Facility Inspections.

Therefore, DRM defers comment on the need for a REMS at this time. A discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the Complete Response letter. Please send DRM a new consult request at such time. This memo serves to close the existing consult request for Nexobrid (concentrate of proteolytic enzymes enriched in bromelain gel), BLA 761192.

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/s/

YASMEEN I ABOU-SAYED
06/15/2021 02:45:46 PM

JACQUELINE E SHEPPARD
06/15/2021 02:49:36 PM

DORIS A AUTH
06/15/2021 02:50:03 PM