Date: 14 July 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

NexoBrid

International nonproprietary name: concentrate of proteolytic enzymes enriched in bromelain

Pharmaceutical form: powder and gel for gel

Dosage strength(s): 0.09 g/g

Route(s) of administration: topical use

Marketing Authorisation Holder: Triskel Integrated Services SA

Marketing Authorisation No.: 68012

Decision and Decision date: approved on 21 April 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DPT	Deep partial thickness
ECG	Electrocardiograph
EMA	European Medicines Agency
ER	Eschar removal
ERA	Environmental Risk Assessment
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FT	Full thickness
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SD	Standard deviation
SOC	Standard of care
SPT	Superficial partial thickness
SwissPAR	Swiss Public Assessment Report
$t_{1/2}$	Half life
TBSA	Total body surface area
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum observed plasma/serum concentration of drug

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TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TWs	Target wounds

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance concentrate of proteolytic enzymes enriched in bromelain of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Drug Status was granted on 29 September 2020.

2.2 Indication and Dosage

2.2.1 Requested Indication

NexoBrid is indicated for treatment of eschar in adults with deep partial and full-thickness thermal burns.

2.2.2 Approved Indication

NexoBrid is indicated for removal of eschar in adults with deep partial and full-thickness thermal burns.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
NexoBrid should only be applied by trained healthcare professionals in specialist burn centres.
A layer 1.5 to 3 millimetres thick of NexoBrid gel is applied to a burn wound area of 2.5% of the total body surface area (TBSA) of an adult.
NexoBrid should not be applied to more than 15% TBSA (see also Warnings and precautions, Coagulopathy).
NexoBrid should be left in contact with the burn for a duration of 4 hours. There is very limited information on the use of NexoBrid on areas where eschar remained after the first application.
A second and subsequent application is not recommended.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	23 December 2020
Formal control completed	20 January 2021
List of Questions (LoQ)	8 July 2021
Answers to LoQ	6 October 2021
Predecision	23 December 2021
Answers to Predecision	21 February 2022
Final Decision	12 April 2022
Decision	approval

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3 Medical Context

Burns, which might be due to various causes (e.g. fire, chemical, contact), are processes that will induce the coagulation and necrosis of tissues. Early removal of these tissues, also known as eschar, is of importance in order to prevent subsequent local and systemic complications (scarring, infection, sepsis), allow for clinical visual evaluation of burn severity and depth, and preserve viable tissue.

Depending on the depth of the lesion, burns are classified as:

1st degree:	Only the epidermis is involved
2nd degree superficial:	Extends into the superficial dermis (superficial partial thickness, SPT)
2nd degree deep:	Extends into the deep dermis (deep partial thickness, DPT)
3rd degree:	Full thickness (FT) of the cutaneous tissue (i.e. through the whole dermis and into subcutaneous structures)
4th degree:	Extends through the entire skin, into underlying fat, muscle and bone

Whereas 1st and 2nd degree superficial burns will spontaneously heal without scars, 2nd degree deep, 3rd degree and 4th degree burns will require debridement and grafting.

Standard of care (SOC) for burn eschar removal relies primarily on surgical tangential excision to mechanically remove the eschar. This well-established technique is relatively nonselective and might result in the excision of viable dermal tissue, thereby increasing the surface area needed for autografting along with increased risk of scar formation and functional compromise.

NexoBrid is composed of (i) a concentrate of proteolytic enzymes enriched in bromelain extracted from the stem of the pineapple plant (*Ananas comosus* [L.] Merr.) that has been sterile filtered and lyophilised and (ii) a gel vehicle (Carbomer, dibasic sodium phosphate and purified water). After application of the NexoBrid mixture to the burn wound, it will degrade and dissolve the burn wound eschar and non-viable tissues. The specific components responsible for this effect have not been identified.

4 Quality Aspects

4.1 Drug Substance

The starting material is pineapple plant stems. Bromelain SP, a drug substance intermediate, is an extract from pineapple plant stems that is processed to yield NexoBrid drug substance. The drug substance consists mainly of protein and saccharides. The protein is a mixture of mainly proteases. The two major proteases are stem bromelain and ananain. The remaining constituents consist of buffer components, water and small molecule metabolites.

A batch of drug substance is defined as a single production run, which may utilise multiple batches of intermediate drug substance (Bromelain SP). The manufacturing process is divided into two main stages: In the first stage, the intermediate drug substance Bromelain SP is obtained through crushing, sedimentation, concentration, filtration and lyophilisation and then, in the second stage, processed through a number of filtration and purification steps to yield the drug substance. Based on an analysis of the nature of the drug substance and the manufacturing process, pH and temperature were identified as critical operational parameters.

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The drug substance manufacturing process was validated at two manufacturing scales. The validation batches were manufactured consecutively and independently, and were monitored for in-process control parameters, performance parameters, process yield, batch release quality control tests and quality of the incoming drug substance intermediate.

The drug substance has been characterised for description, purity, quantity and other tests such as pH and tests for microorganisms. All the analytical methods are described, and non-compendial methods have been validated in accordance with ICH guidelines. Since the drug substance is not stable for extended periods of storage, the potency is evaluated by determining the potency of NexoBrid drug product. The drug product is a lyophilised powder and is stable for extended periods of time.

Batch analysis includes all batches that have been used for clinical trials and stability studies since the drug substance definition was introduced in 2008.

The drug substance is held in a cooled (10 ± 1°C) glass vessel. This hold step has been validated as part of the overall manufacturing validation.

4.2 Drug Product

NexoBrid drug product consists of a lyophilised powder containing either 2 g or 5 g NexoBrid drug substance, presented in 50 mL glass vials, and a gel vehicle used to mix the powder, presented in 150 mL glass bottles. The gel vehicle is described in a separate 3.2.P. One vial of drug product and one bottle of gel vehicle of the corresponding size are supplied together in a cardboard box.

The manufacturing process for the drug product consists of dilution of the drug substance, sterile filtration, aseptic filling into sterile lyophilisation trays and lyophilisation. The bulk lyophilised powder in trays is produced within hours after the bulk drug substance manufacture. The powder filling process is followed by stoppering the vials with rubber stoppers and capping with aluminium tear-off caps, labelling and packaging.

Process consistency was established based on production of three consecutive independent runs of bulk lyophilised powder in trays using the x 2 manufacturing scale and the lyophilisation cycle of the 5 g presentation. These batches in trays were used for filling of five consecutive batches of drug product: two batches of 2 g and three batches of 5 g presentation.

The drug product powder has been characterised for description, identification, purity, potential contaminants, content, potency, impurities, excipient testing and other tests such as water content, sterility, pH, time to dissolution and uniformity of dosage units. The drug product and gel vehicle mixture has been characterised for appearance, pH, homogeneity, viscosity and reconstitution time. All the analytical methods are described, and non-compendial methods have been validated in accordance with ICH guidelines.

The drug product batches analysis presented both the 2 g and 5 g drug product presentations. These include all batches that have been used for clinical trials and stability studies.

The primary container closure system for both 2 g and 5 g drug product consists of a 50 mL clear, type II glass vial closed with a siliconised bromobutyl rubber stopper and sealed with an aluminium overcap.

The drug product is stored at 2-8°C. No significant changes were observed within the proposed storage conditions. A shelf life of 36 months has been accepted. The gel vehicle is stored at 2-8°C. A shelf life of 36 months has been accepted.

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4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The drug product shelf life is supported by data from recommended storage conditions, as well as accelerated and photostability studies.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for NexoBrid, the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the EMA CHMP assessment report of 20 September 2012 that was provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of NexoBrid in the proposed indication. The submitted nonclinical documentation is comparable to the dossier assessed by the EU CHMP in 2012. No new nonclinical data have been generated since then. The pharmaco-toxicological profile has been sufficiently characterised.
The single and repeat-dose toxicity studies showed the potential of NexoBrid to interfere with the clotting system after intravenous administration. This effect has not been observed in clinical practice up to now.
The developmental toxicity studies conducted in rats and rabbits showed no signs of embryo-foetal toxicity of NexoBrid in the absence of clear maternal toxicity. As rats and rabbits are particularly sensitive to systemically administered NexoBrid, the doses and resulting exposures investigated in these studies were considerably lower than those maximally reported in the clinical setting. Therefore, the true potential of NexoBrid to interfere with embryo-foetal development in humans could not be fully evaluated.
Based on the findings from a standard battery for genotoxicity testing, NexoBrid does not show relevant genotoxic potential.
It is unknown whether NexoBrid or its metabolites are excreted into human breast milk. A risk to the suckling child cannot be excluded. The recommendation to discontinue breastfeeding during treatment and for four days following completion of therapy is considered appropriate.
All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data in this application has been partly carried out in reliance on previous regulatory decisions, available assessment reports and product information texts issued by the EMA. For aspects of the assessment not covered in this SwissPAR, reference is made to the publicly available assessment report for Nexobrid EMA/648483/2012.

New pharmacological data from the second pivotal phase 3 study MW 2010-03-02 has been specifically evaluated for this application.

ADME

Absorption

Across studies, NexoBrid is generally rapidly absorbed, with a median T_{max} value at 4 hours (during the duration of treatment application). After one application, C_{max} in the first MW2008-09-03 study was 800±640 ng/mL, whereas in the most recent study MW2010-03-02, it was 200±184 ng/mL. The AUC_{0-4} in the MW2008-09-03 study was 1930±648 h*ng/mL, whereas it was 516±546 h*ng/mL in study MW2010-03-02. After two applications, the C_{max} after the first and second application are comparable in the same study, and only slight accumulation is seen in AUC_{0-4} (2130±1570 h*ng/mL vs 1930±648 h*ng/mL for study MW2008-09-03 and 618 h*ng/mL vs 516±546 h*ng/mL for study MW2010-03-02).

In both studies, there was a statistically significant correlation between serum C_{max} and AUC_{0-4} values versus percentage of total body surface area (%TBSA). In study MW2010-03-02, a comparison by wound depth of the dose-normalised serum C_{max} and AUC_{0-4} values suggested that the depth of the NexoBrid-treated wound has negligible impact on systemic exposure.

The median terminal half-life in study MW2008-09-03 was 12±4.4 hours. Values ranged between 12 and 17 hours, supporting the decreased presence of NexoBrid in serum at 72 hours post treatment. No $t_{1/2}$ data was provided in study MW2010-03-02 or its supplementary ADME report. The reason for this was that fewer than half of the patients had sufficient data as defined in the pharmacokinetic analysis plan to reliably determine a terminal elimination rate constant (λz) that is used for $t_{1/2}$ estimation.

Regarding C_{max}, in previous Phase II and initial Phase III studies, a high variability (up to a factor of 10) of measurements was attributed to the fact that analyses were performed at two different laboratories as well as possible differences in sampling times. Based on the highest C_{max} value obtained from clinical samples (13,500 ng/mL) in previous studies, in relation to the dose at which toxicity was seen in animal models, NexoBrid application was restricted to a single application, with a maximum of 15% of total body surface area. The most recent MW2010-03-02 data were analysed at a single site. These showed a substantially lower C_{max} of 200±184 ng/mL. This variability was essentially justified by the applicant by laboratory method changes as well as a lower dose of NexoBrid used in the second Phase 3 study. Nevertheless, the recommendation that in principle a single application covering a maximum of 15% of total body surface area be used is still justified.

Interactions

Since it is a topical product, interaction with food is not applicable. There are no clinical or nonclinical studies addressing systemic drug interactions. Nonclinical studies showed that silver sulfadiazine and povidone-iodine negatively influenced the debriding activity of the bromelain extract. Prior to NexoBrid treatment, the wound bed is soaked for a minimum of 2 hours with antibacterial solution and all local medications are removed. Therefore, there is a low possibility of local drug-drug interactions.

NexoBrid essentially displayed CYP2C8 and CYP2C9 time-dependent inhibition in human hepatocytes. The clinical relevance of this observation is unclear since the concentrations of NexoBrid in the

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incubation mixtures and those measured in clinical serum samples are not directly comparable. In addition, as the product is administered topically for a single 4-hour application, these observations may not be clinically meaningful for NexoBrid.

Pharmacodynamics

NexoBrid is a concentrate of proteolytic enzymes extracted from pineapple and enriched in bromelain. It is a debriding agent applied topically for removal of eschar in 2nd and 3rd degree deep partial and full-thickness burns. The mixture of enzymes in NexoBrid dissolves burn wound eschar; the specific components responsible for this effect have not been identified.

6.2 Dose Finding and Dose Recommendation

Study MW 2001-10-03 was an open label, observer-blinded, randomised, multicentre, dose-ranging study. The study was designed to evaluate the efficacy and safety of three NexoBrid doses (1 g, 2 g and 4 g per 20 g of gel vehicle) in the treatment of patients with partial deep dermal and/or full-thickness burns.

The mean time to >95% epithelialisation from last debridement was 21.2 ± 2.4 days, 13.0 ± 6.7 days and 19.0 ± 8.5 days, for the 1 g, 2 g and 4 g NexoBrid treatment groups, respectively. The median time to >95% epithelialisation from last debridement was 20.0, 11.5 and 16.0 days for the 1 g, 2 g and 4 g NexoBrid treatment groups, respectively. NexoBrid at 1 g, 2 g and 4 g removed 98.9%, 100% and 99.1% of the eschar, respectively.

In this study, the 1 g dose showed results in the removal of eschar similar to those observed for the 2 g and 4 g doses. However, the 2 g dose provided a safety margin in comparison to the 1 g dose for achieving efficacious treatment in more severe or difficult to treat burns than those of the patients in this study. There was no difference observed in safety measurements among the three treatment groups.

6.3 Efficacy

The evaluation of the clinical efficacy data in this application has been partly carried out in reliance on previous regulatory decisions, available assessment reports and product information texts issued by the EMA. For aspects of the assessment not covered in this SwissPAR, reference is made to the publicly available assessment report for Nexobrid EMA/648483/2012. New efficacy data from the pivotal Phase 3 study MW2010-03-02 were evaluated for the present application.

Study MW 2010-03-02 (DETECT) was a pivotal multicentre, multinational, randomised, 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 (SOC).

Eligible patients were stratified according to the patient's percentage total body surface area (% TBSA), overall depth of target wounds (TWs) and centre. Following the stratification, patients were randomised as per their stratification group in a 3:3:1 ratio to the study treatments of NexoBrid : SOC : gel vehicle. Following eschar removal procedures, patients were treated in accordance with post-eschar removal wound care strategies and underwent daily assessments of vital signs and pain until hospital discharge. After hospital discharge, patients were followed up until complete wound closure was achieved and confirmed, and 2 weeks later for status of each of the patient's TWs. Long-term follow-up visits were performed at 1, 3, 6 and 12 months and will be performed at 18 and 24 months post-last wound closure confirmation visit.

The primary efficacy endpoint of study MW 2010-03-02 was the incidence of complete eschar removal at the end of the topical agent soaking period, as evaluated by a blinded assessor. Secondary efficacy

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endpoints included the reduction of surgical need for excisional eschar removal (ER), the time when complete ER was achieved and blood loss quantification.

Overall, for the full analysis set (FAS) 175 patients were included: 75 in the NexoBrid, 75 in the SOC and 25 in the gel vehicle (placebo) treatment arms. Of the patients randomised in the study, 67/75 (89.33%) patients in the NexoBrid, 63/75 (84%) in the SOC and 23/25 (92%) in the gel vehicle treatment arms completed the acute phase. 57/75 (76%) patients in the NexoBrid, 58/75 (77%) in the SOC and 20/25 (80%) in the gel vehicle treatment arms completed the 12-month follow-up period. Overall, patients' age, BMI, gender and race were similar in all treatment arms. The majority (70%) of patients were males. In study MW 2010-03-02, in the NexoBrid and SOC arms, the mean (SD) %TBSA of all TW was of 6.3 (3.68) and 5.9 (3.06), respectively. Overall TW depth (percentage of DPT vs FT vs mixed) in the NexoBrid and SOC arms was of 45.3%, 2.7%, 52% and 48%, 5.3%, 46.7%, respectively.

For the primary efficacy endpoint, the incidence rate of complete eschar removal in the NexoBrid treatment arm (93%, 70/75 patients) was significantly higher than in the gel vehicle treatment arm (4%, 1/25 patients). Regarding the secondary endpoints, patients treated with NexoBrid demonstrated a significantly lower incidence of surgical excisional compared with patients treated with SOC (4% [3/75] vs 72% [54/75], respectively). Patients treated with NexoBrid demonstrated a shorter time to achieve complete eschar removal in comparison with patients treated with SOC (Kaplan-Meier estimated median time to complete eschar removal of 1.02 days vs. 3.83 days in the NexoBrid and SOC groups, respectively; mean time to complete eschar removal 1.15 ± 0.84 days vs 6.52 ± 8.43 days in the NexoBrid and SOC groups, respectively). Patients treated with NexoBrid suffered less blood loss during the ER procedure compared with patients treated with SOC, with a mean blood loss during ER of 14.17±512 mL in the NexoBrid arm vs 814.51±1020 mL in the SOC arm.

6.4 Safety

In the clinical development programme, 467 patients were treated with NexoBrid in 8 clinical studies (454 patients treated with the 2 g dose). The most relevant safety data comes from the two pivotal Phase 3 studies (MW 2010-03-02 and MW 2004-11-02).

In these, 177 patients were treated with NexoBrid, 149 with SOC and 24 with the gel vehicle (placebo). The large majority (approx. 90%) of NexoBrid-treated patients received one application and had a TW of less than 15% of the total body surface are.

The AE profile for NexoBrid in the treatment of deep partial-thickness (DPT) and full-thickness (FT) burns was similar to SOC and placebo. The most frequently reported AEs were pruritus (NexoBrid 15.3%, SOC 12.8%, placebo 12.5%), pyrexia (NexoBrid 11.9%, SOC 8.7%, placebo 8.3%) and anaemia (NexoBrid 6.2%, SOC 5.4%, placebo 0%). Serious AEs were 8.5% (15/177) in the NexoBrid arm, 6.7% (10/149) in the SOC arm and 12.5% (3/24) in the placebo arm. By MedDRA preferred term, the incidence of all serious TEAEs in the NexoBrid and SOC arms was <2%, representing single events. Only two events occurred in more than one patient : three patients with sepsis and two patients with bacterial wound infection in the NexoBrid group. Regarding deaths, data from Phase 2 and the first Phase 3 study MW 2004-11-02 showed a higher number of deaths in the NexoBrid (n=5) vs the SOC (n=1) arm. In the pivotal study MW 2010-03-02, two deaths occurred in the NexoBrid group, and none in the SOC or placebo arms. All deaths were reviewed by a data safety monitoring board (DSMB), the investigator and the sponsor, and none are considered as related to NexoBrid treatment.

In study MW 2010-03-02, long-term follow-up in the period following the acute phase (≥3 and up to 12 months post wound closure) showed that the most frequent AEs included pruritus (5.2% NexoBrid, 2.9% SOC, 0% placebo), decreased joint range of motion (2.6% NexoBrid, 4.4% SOC, 16.7% placebo) and hypertrophic scar (0% NexoBrid, 2.9% SOC, 0% placebo). Two patients in the NexoBrid arm experienced a TEAE (folliculitis and pruritus) assessed by the investigator as related to the study drug. Seven patients (four NexoBrid and three SOC) experienced SAEs that were not considered as

related to the study drug. One patient in the NexoBrid arm died during the long-term follow-up due to an unknown cause that was considered not related to the study drug.

The cardiac safety of NexoBrid was addressed in a report provided with study MW 2010-03-02. It indicated that there was no effect of NexoBrid on heart rate, atrioventricular conduction, cardiac depolarisation or repolarisation, and no clinically relevant ECG morphological changes demonstrating a signal of concern. Nevertheless, more tachycardia as well as ST depression events were recorded in the NexoBrid treatment group. Morphologic findings were deemed not clinically significant and linked to tachycardia due to the potential increased pain during NexoBrid treatment, since the patients treatment is removed at the 4 hours timepoint. The applicant proposed to strengthen the required pain management regarding adequate analgesia and/or anaesthesia.The active ingredient in NexoBrid, bromelain, is anticipated to be immunogenic in humans. Exposure can follow topical administration or the drug or can be pre-existent due to dietary consumption of pineapple. NexoBrid treatment may therefore induce formation of anti-drug antibodies (ADA). The evaluation of immunogenicity involved ADA testing of samples collected from study MW2010-03-02. In the evaluable population, a high proportion (40.3%, 25/62) of patients in the NexoBrid treatment arm had a positive ADA result at baseline. The incidence of treatment-emergent ADA (treatment-induced or treatment-boosted) was 93.5% (58/62). All patients with results available at the 24-month post-treatment time point (n=21) were ADA positive, indicating the persistent nature of ADA. The incidence of hypersensitivity reactions, including allergic reactions and cases of rash assessed as possibly related to NexoBrid, was approximately 5% (4/77) of treated patients, and reactions were mild-moderate in intensity. No clear relationship could be established between the presence of ADA pre-treatment and hypersensitivity reactions. No cases of anaphylaxis were reported in the study. Importantly, in the ADA evaluable population, there was no obvious relationship between lack of NexoBrid efficacy and the presence of ADA at baseline.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Second degree deep partial-thickness as well as third degree burns require early removal of necrotic tissue before further wound care can be performed (spontaneous re-epithelialisation or autografting). Burn eschar removal relies primarily on surgical tangential excision, which is a well-established technique but relatively nonselective and might result in the excision of viable dermal tissue, thereby increasing the surface area needed for autografting.

The efficacy of NexoBrid to remove the eschar tissue as well as the reduction in the need for further surgical excisions was established in two Phase 3 pivotal studies. There was a reduction in the need for and surface of autografts for 2nd degree deep partial-thickness wounds in both studies, but the difference in the second study was not statistically significant. The benefit of NexoBrid for the treatment of full-thickness wounds (3rd degree) lies solely in the efficacy of eschar tissue debridement, and not a reduction in autografts, since there are no more viable dermal tissue remnants that might be the nucleus for re-epithelialisation. Long-term follow-up for cosmesis, quality of life and function were similar for NexoBrid and standard of care, indicating no deleterious effect of the method. NexoBrid might be of interest (i) in debriding areas of special functional interest where it is of major importance to preserve all undamaged tissue (ii) in patients where surgical excision may not be possible due to the general condition and co-morbidities and (iii) as an alternative to the surgical excision when treatment needs to be performed without immediate availability of qualified burns surgeons.

The most frequently reported treatment-related AEs in the NexoBrid group were pyrexia, pain and tachycardia. Important safety outcomes identified by the EMA in the initial 2012 evaluation that were to be followed up in the second pivotal study MW 201-03-02 (blood loss, blood transfusions and coagulation parameters, graft failure, time to wound closure, immunogenicity and death) revealed no specific concerns. Cardiac safety was studied in the second pivotal study, and data showed an increase in tachycardia events as well as repolarisation changes in the NexoBrid treatment arm.

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Additional information showed that cardiac events were balanced between treatment groups and that the timing of the events indicate that these are not directly related to the drug but to the burn management process.

Based on the demonstrated efficacy and the safety profile, the benefit-risk profile of NexoBrid is positive. It provides an alternative non-surgical debridement method consisting of proteolytic enzymes that are topically applied and will dissolve the burn wound eschar and non-viable tissues. NexoBrid does not in itself change the care concepts for burn wounds but might be of particular interest (i) in debriding areas of special functional interest (e.g. hands or face) where it is of major importance to preserve all undamaged tissue (ii) in patients where surgical excision may not be possible due to the general condition and co-morbidities and (iii) as an alternative to the surgical excision when treatment needs to be performed without immediate availability of qualified burns surgeons.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to NexoBrid, powder and gel for gel, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

NexoBrid 5 g

Composition

Active substances

Concentrate of proteolytic enzymes enriched in bromelain (stem bromelain).
The proteolytic enzymes are a mixture of enzymes from the stem of *Ananas comosus* (pineapple plant).

Excipients

NexoBrid powder
Ammonium sulphate
Acetic acid
Gel
Carbomer 980
disodium phosphate
Sodium hydroxide
Water for injections

Pharmaceutical form and active substance quantity per unit

Powder and gel for gel.
The powder is off-white to light tan. The gel is clear and colourless.
One vial of NexoBrid 5 g contains 5 g of concentrate of proteolytic enzymes enriched in bromelain, corresponding to 0.09 g/g concentrate of proteolytic enzymes enriched in bromelain after mixing (or 5 g/55 g gel).

Indications/Uses

NexoBrid is indicated for removal of eschar in adults with deep partial- and full-thickness thermal burns.

Dosage/Administration

NexoBrid should only be applied by trained healthcare professionals in specialist burn centres.
5 g NexoBrid powder in 50 g gel is applied to a burn wound area of 2.5 % Total Body Surface Area (TBSA) of an adult, with a gel layer thickness of 1.5 to 3 mm.

NexoBrid should not be applied to more than 15% TBSA in one session (see also section “Warnings and precautions”, Coagulopathy).
NexoBrid should be left in contact with the burn for a duration of 4 hours. There is very limited information on the use of NexoBrid on areas where eschar remained after the first application.
A second and subsequent application is not recommended.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients with impaired hepatic function

There is no information on the use of NexoBrid in patients with hepatic impairment. These patients should be carefully monitored.

Patients with impaired renal function

There is no information on the use of NexoBrid in patients with renal impairment. These patients should be carefully monitored.

Elderly patients

Experience with NexoBrid in elderly patients (>65 years) is limited. Benefit/risk assessment should include consideration of the greater frequency of concomitant disease or other medicinal product therapy in the elderly. No dose adjustment is required.

Children and adolescents

The safety and efficacy of NexoBrid in children and adolescents younger than 18 years have not yet been established.
NexoBrid is not indicated for use in patients younger than 18 years.

Mode of administration

Cutaneous use.
Before use, the powder must be mixed with the gel producing a uniform gel.
NexoBrid should be applied to a clean, keratin-free (blisters removed), and moist wound area.
Topically applied medicinal products (such as silver sulfadiazine or povidone-iodine) at the wound site must be removed and the wound must be cleansed prior to NexoBrid application.
See section “Other information/Instructions for handling” for instructions on NexoBrid gel preparation.

Preparation of patient and wound area

A total wound area of not more than 15% TBSA can be treated with NexoBrid (see also section “Warnings and precautions”, Coagulopathy).

- Enzymatic debridement might be a painful procedure and requires adequate analgesia and/or anesthesia. Pain management must be used as commonly practiced for an extensive dressing change; it should be initiated at least 15 minutes prior to NexoBrid application.
- The wound must be cleaned thoroughly and the superficial keratin layer or blisters removed from the wound area, as the keratin will isolate the eschar from direct contact with NexoBrid and prevent eschar removal by NexoBrid.
- Dressing soaked with an antibacterial solution (e.g 0.05-0.5%Chlorhexidine, sodium hypochlorite [Dakin's solution] or hypertonic 5-10 % saline solution) must be applied for 2 hours. Silver sulfadiazine and povidone-iodine should not be used.
- All topically applied antibacterial medicinal products must be removed before applying NexoBrid. Remaining antibacterial medicinal products may interfere with the activity of NexoBrid by decreasing its efficacy.
- The area from which you wish to remove the eschar must be surrounded with a sterile paraffin ointment adhesive barrier by applying it a few centimetres outside of the treatment area (using a dispenser). The paraffin layer must not come into contact with the area to be treated to avoid covering the eschar, thus isolating the eschar from direct contact with NexoBrid.
- To prevent possible irritation of abraded skin by inadvertent contact with NexoBrid and possible bleeding from the wound bed, acute wound areas such as lacerations or escharotomy incisions should be protected by a layer of a sterile fatty ointment or fatty dressing (e.g. petrolatum gauze).
- Sterile isotonic sodium chloride 9 mg/ml (0.9%) solution must be sprinkled on the burn wound. The wound must be kept moist during the application procedure.

NexoBrid application

- Within 15 minutes of mixing (see "Other information/ Instructions for handling"), NexoBrid must be applied topically to the moistened burn wound, at a thickness of 1.5 to 3 millimetres.
- The wound must then be covered with a sterile occlusive film dressing that adheres to the sterile adhesive barrier material applied as per the instruction above (see Preparation of patient and wound area). The NexoBrid gel must fill the entire occlusive dressing, and special care should be taken not to leave air under this occlusive dressing. Gentle pressing of the occlusive dressing at the area of contact with the adhesive barrier will ensure adherence between the occlusive film and the sterile adhesive barrier and achieve complete containment of NexoBrid on the treatment area.
- The dressed wound must be covered with a loose, thick fluffy dressing, held in place with a bandage.
- The dressing must remain in place for 4 hours.

Removal of NexoBrid

- Appropriate preventive analgesia medicinal products must be administered.

- After 4 hours of NexoBrid treatment, the occlusive dressing must be removed using aseptic techniques.
- The adhesive barrier must be removed using a sterile blunt-edged instrument (e.g., tongue depressor).
- The dissolved eschar must be removed from the wound by wiping it away with a sterile blunt-edged instrument.
- The wound must be wiped thoroughly first with a large sterile dry gauze or napkin, followed by a sterile gauze or napkin that has been soaked with sterile isotonic sodium chloride 9 mg/ml (0.9%) solution. The treated area must be rubbed until the appearance of a pinkish surface with bleeding points or a whitish tissue. Rubbing will not remove adhering undissolved eschar in areas where the eschar still remains.
- A dressing soaked with an antibacterial solution (e.g 0.05-0.5%Chlorhexidine, sodium hypochlorite [Dakin's solution] or hypertonic 5-10 % saline solution) must be applied for an additional 2 hours.

Wound care after debridement

- The debrided area must be covered immediately by temporary or permanent skin substitutes or dressings to prevent desiccation and/or formation of pseudoeschar and/or infection.
- Before a permanent skin cover or temporary skin substitute is applied to a freshly enzymatically debrided area, a soaking wet-to-dry dressing must be applied.
- Before application of the grafts or primary dressing, the debrided bed must be cleaned and refreshed by, e.g., brushing or scraping to allow dressing adherence.
- Wounds with areas of full-thickness and deep burn should be autografted as soon as possible after NexoBrid debridement. Careful consideration should also be given to placing permanent skin covers (e.g. autografts) on deep partial thickness wounds soon after NexoBrid debridement.
  See section "Warnings and precautions".

Each NexoBrid vial, gel, or reconstituted gel should be used for a single patient only.

Contraindications

Hypersensitivity to the active substance, to pineapples or papain (see also section "Warnings and precautions"), or to any of the excipients listed in section "Excipients".

Warnings and precautions

Absorption and burn wounds for which NexoBrid is not recommended

Concentrate of proteolytic enzymes enriched in bromelain is systemically absorbed from burn wound areas (see section "Pharmacokinetics").

NexoBrid is not recommended for use on:

- penetrating burn wounds where foreign materials (e.g. implants, pacemakers, and shunts) and/ or vital structures (e.g. larger vessels, eyes) are or could become exposed during debridement.
- chemical burn wounds.
- application in cavities (such as cavitas peritonealis or cavitas pleuralis)
- wounds contaminated with radioactive and other hazardous substances to avoid unforeseeable reactions with the product and an increased risk of spreading the noxious substance.

Use in patients with cardiopulmonary and pulmonary disease

NexoBrid should be used with caution in patients with cardiopulmonary and pulmonary disease, including pulmonary burn trauma and suspected pulmonary burn trauma.

General principles of proper burn wound care must be adhered to when using NexoBrid. This includes proper wound cover for the exposed tissue.

Burns for which there is limited or no experience

There is no experience of the use of NexoBrid on:

- perineal and genital burns.
- electrical burns.

There is limited information on the use of Nexobrid on facial burn wounds. There are literature reports of successful use of NexoBrid on facial burn wounds, but the use of NexoBrid on facial burn wounds should only be considered by professionals with significant experience in enzymatic debridement procedures.

NexoBrid must be used with caution in such patients. Eyes should be carefully protected during treatment of facial burns using fatty ophthalmic ointment on the eyes and adhesive barrier petroleum ointment around to insulate and cover the eyes with occlusive film.

Prevention of wound complications

In NexoBrid studies wounds with visible dermal remnants were allowed to heal by spontaneous epithelialisation. In several cases adequate healing did not occur, and autografting was required at a later date, leading to delays in wound closure which may be associated with increased risk of wound-related complications. Therefore, wounds with areas of full-thickness and deep burn should be autografted as soon as possible after NexoBrid debridement (see section “Clinical efficacy” for study results). Careful consideration should also be given to placing permanent skin covers (e.g. autografts) on deep partial thickness wounds soon after NexoBrid debridement. See also section “Dosage/Administration” and “Undesirable effects”.

As in the case of surgically debrided bed, in order to prevent desiccation and/or formation of pseudoeschar and/or infection, the debrided area should be covered immediately by temporary or permanent skin substitutes or dressings. When applying a permanent skin cover (e.g., autograft) or temporary skin substitute (e.g., allograft) to a freshly enzymatically debrided area, care should be taken to clean and refresh the debrided bed by, e.g., brushing or scraping to allow dressing adherence.

Eye protection

Direct contact with the eyes should be avoided. If there is a risk of eye contact, the patient's eyes should be protected with fatty ophthalmic ointment.

In case of eye exposure, irrigate exposed eyes with copious amounts of water for at least 15 minutes.

Hypersensitivity reactions, skin exposure, inhalation

There have been reports of serious allergic reactions including anaphylaxis (with manifestations such as rash, erythema, hypotension, tachycardia) in patients undergoing debridement with NexoBrid. In these cases, a causal relationship to NexoBrid was considered possible but a relationship to concomitant medications could not be ruled out.

Allergic reactions to inhaled bromelain have been reported in the literature (including anaphylactic reactions and other immediate-type reactions with manifestations such as bronchospasm, angiooedema, urticaria, and mucosal and gastrointestinal reactions). No occupational hazard was found in a study assessing the amount of airborne particles during NexoBrid Gel preparation. Still, appropriate handling of the debriding agent (including wearing of gloves and protective clothing as well as a surgical mask) is mandatory.

The potential of NexoBrid (a protein product) to cause sensitisation should be taken into account when re-exposing patients to bromelain-containing products at a later point in time. The use of NexoBrid in subsequent burn injury is not recommended.

In case of skin exposure, NexoBrid should be rinsed off with water to reduce the likelihood of skin sensitisation (see section "Instructions for handling").

Cross-sensitivity

Cross-sensitivity between bromelain and papain as well as latex proteins (known as latex-fruit syndrome), bee venom, and olive tree pollen has been reported in the literature.

Coagulopathy

A reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported in the literature as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. During the clinical development of NexoBrid, there was no indication of an increased bleeding tendency or bleeding at the site of debridement.

NexoBrid should be used with caution in patients under anticoagulant therapy or other drugs affecting coagulation and in patients with disorders of coagulation, low platelet counts and increased risk of bleeding from other causes e.g. peptic ulcers and sepsis.

Patients should be monitored for possible signs of coagulation abnormalities and signs of bleeding.

Monitoring

In addition to routine monitoring for burn patients (e.g., vital signs, volume/water/electrolyte status, complete blood count, serum albumin and hepatic enzyme levels), patients treated with NexoBrid should be monitored for:

- Rise in body temperature.
- Signs of local and systemic inflammatory and infectious processes.
- Conditions that could be precipitated or worsened by analgesic premedication (e.g., gastric dilatation, nausea and risk of sudden vomiting, constipation) or antibiotic prophylaxis (e.g., diarrhoea).
- Signs of local or systemic allergic reactions.
- Potential effects on haemostasis (see above).

Removal of topically applied antibacterial medicinal products before NexoBrid application

All topically applied antibacterial medicinal products must be removed before applying NexoBrid. Remaining antibacterial medicinal products may interfere with the activity of NexoBrid by decreasing its efficacy.

Interactions

No interaction studies with NexoBrid have been performed.

Reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. Caution and monitoring is therefore needed when prescribing concomitant medicinal products that affect coagulation. See also section “Warnings and precaution”.

NexoBrid, when absorbed, is an inhibitor of cytochrome P 450 2C8 (CYP2C8) and P450 2C9 (CYP2C9). This should be taken into account if NexoBrid is used in patients receiving CYP2C8 substrates (including amiodarone, chloroquine, fluvastatin, paclitaxel, pioglitazone, repaglinide, sorafenib and torasemide) and CYP2C9 substrates (including ibuprofen, losartan, celecoxib, warfarin, and phenytoin).

Topically applied antibacterial medicinal products (e.g. silver sulfadiazine or povidone iodine) may decrease the efficacy of NexoBrid (see section “Warnings and precaution”).

Bromelain may enhance the actions of fluorouracil and vincristine. Patients should be monitored for increased toxicity.

Bromelain may enhance the hypotensive effect of angiotensin convertin enzyme (ACE) inhibitors, causing larger decreases in blood pressure than expected. Blood pressure should be monitored in patients receiving ACE inhibitors.

Bromelain may increase drowsiness caused by some medicinal products (e.g., benzodiazepines, barbiturates, narcotics and antidepressants). This should be taken into account when dosing such products.

Pregnancy, lactation

Pregnancy

There are no data from the use of NexoBrid in pregnant women.

Animal studies are insufficient to properly assess the potential of NexoBrid to interfere with embryonal/foetal development (see section ”Preclinical data”).
Since the safe use of NexoBrid during pregnancy has not yet been established, NexoBrid is not recommended during pregnancy.

Lactation

It is unknown whether concentrate of proteolytic enzymes enriched in bromelain or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued at least 4 days from NexoBrid application initiation.

Fertility

No studies were performed to assess the effects of NexoBrid on fertility.

Effects on ability to drive and use machines

Not relevant.

Undesirable effects

In the clinical development program, 467 patients have been treated with NexoBrid in eight clinical studies, including 2 open-label, randomized, controlled Phase 3 clinical trials. The main safety evaluation is based on the integrated analysis of data from these 2 phase 3 studies involving 177 patients treated with NexoBrid.
The most commonly reported adverse reactions of the use of NexoBrid are transient pyrexia/hyperthermia (reported in 15.3% of patients treated with NexoBrid) and pain (4.5%).
The serious adverse reactions by preferred term, reported in more than one patient (≥1.1%) were sepsis and wound infection bacterial. Adverse Reaction are detailed below.
The following definitions apply to the frequency terminology used hereafter:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)
The frequencies of the adverse reactions presented below reflect the use of NexoBrid to remove eschar from deep partial- or full-thickness burns in a regimen with local antibacterial prophylaxis, recommended analgesia, as well as coverage of the wound area after application of NexoBrid for 4 hours with an occlusive dressing for containment of NexoBrid on the wound.
Infections and infestations
Common: Wound infection

Skin and subcutaneous tissue disorders
Common: Wound complication (including wound dessication, wound deepening, wound re-opening, graft loss/graft failure, local hematoma)
General disorders and administration site conditions
Very common: Pyrexia
Common: Local pain
Cardiac disorders
Common: Tachycardia
Immune system disorders
Not known: Serious allergic reactions including anaphylaxis

Description of selected undesirable effects

Immunogenicity
The DETECT study included immunogenicity testing of samples collected prior to and at different times following NexoBrid treatment (baseline, Day 28, Day 56, 6 months, and 24 months).
At baseline, 40.3% (25/62) of subjects tested were positive for antibodies to NexoBrid, which may reflect prior sensitization to pineapple-derived proteins and glycoproteins bearing cross-reactive carbohydrate determinants. The incidence of treatment-emergent antibodies was 93.5% (58/62), which included 62.1% (36/58) subjects who were negative at baseline and 37.9% (22/58) who had at least a four-fold increase in antibody titers post-treatment.
Time of onset of treatment-emergent antibodies (increases in antibody titers), was consistent with an affinity-matured immune response to a xenogeneic protein (100% seroconversion at the 4-week time-point), and the response was persistent.
There was no apparent relationship between maximum post-treatment antibody titer and either the total dose of NexoBrid (grams applied) or TBSA treated. There was no obvious relationship between efficacy (complete eschar removal) and baseline or post-treatment antibody titer. No clear relationship could be established between the presence of antibodies pre-treatment and incidence of hypersensitivity reaction.
Paediatric population
The safety in the paediatric population has not yet been established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Treatment with concentrate of proteolytic enzymes enriched in bromelain prepared in a powder:gel ratio of 1:5 (0.16 g per g of mixed gel) in patients with deep partial- and/or full-thickness burns within the framework of a clinical study did not result in significantly different safety findings when compared to treatment with concentrate of proteolytic enzymes enriched in bromelain prepared in a powder:gel ratio of 1:10 (0.09 g per 1g of mixed gel).
Limited data from clinical trials and post marketing use of NexoBrid at concentration of 0.09 g per 1g of mixed gel did not indicate an increased risk when NexoBrid was used in two applications to a TBSA > 15% (up to 30% TBSA).

Properties/Effects

ATC code

D03BA03
Pharmacotherapeutic group: Preparations for treatment of wounds and ulcers, proteolytic enzymes.

Mechanism of action/Pharmacodynamics

Concentrate of proteolytic enzymes enriched in bromelain is a debriding agent, applied topically for removal of eschar in deep partial- and full-thickness burns.
The mixture of enzymes in NexoBrid dissolves burn wound eschar. The specific components responsible for this effect have not been identified. The major constituent is stem bromelain.

Clinical efficacy

The efficacy and safety of NexoBrid for the debridement of deep partial and full thickness thermal burns were assessed in two pivotal multicenter, multi-national, randomized, controlled phase 3 studies (MW2010-03-02 and MW2004-11-02).
DETECT study (MW2010-03-02)- Phase 3
This study is a multi-center, multi-national, assessor-blinded, randomized, three-arm study aimed at demonstrating superiority of NexoBrid treatment over Gel Vehicle (placebo) control and standard of care (SOC) treatment, in hospitalized adult subjects with deep partial thickness and/or full thickness thermal burn of 3-30% TBSA and total burn wounds of no more than 30% TBSA.
The analyses were planned in stages: First analysis was performed at the end of the Acute Phase (from baseline until 3 months had passed from last patient reached complete wounds closure) and second analysis was performed after the last patient reached the 12M FU visit (12 months period).
A total of 175 subjects were randomized (Intend to Treat cohort) in a 3:3:1 ratio (NexoBrid: SOC: Gel Vehicle), and 169 subjects were treated. Patients in the SOC treatment arm were treated with surgical and/or nonsurgical SOC as per the investigators' discretion.
Overall subject demographics and wound baseline characteristics were comparable across the study arms. The age range in the group treated with NexoBrid was 18 to 75 years, 18 to 72 years in the

SOC group and 18 to 70 years in the Gel Vehicle group. Mean age in all 3 arms was 41 years, and 65%, 79%, and 60% of subjects were male in the NexoBrid, SOC and Gel Vehicle (placebo) arms, respectively. Target Wound (TW) was the burn area to be treated (Eschar Removal) with NexoBrid, SOC or Gel Vehicle. On a patient level, the mean % TBSA of TWs was 6.28% for patients in the NexoBrid treatment arm, 5.91% in SOC, and 6.53% in Gel Vehicle (average of 1.7 TWs per subject). Primary endpoint was incidence of complete (>95%) eschar removal as compared with Gel Vehicle. Secondary endpoints included time to complete eschar removal, reduction in surgical burden, and debridement related blood loss as compared to SOC. Time to complete wound closure, long term cosmesis and function measures by the Modified Vancouver Scar Scale (MVSS) after the 12 months follow-up period were analysed as safety endpoints.
The results of the study show that the incidence rate of complete eschar removal in the NexoBrid treatment arm was significantly higher than in the Gel Vehicle treatment arm.

Incidence of Complete Eschar Removal in the DETECT Study

	NexoBrid (ER/N)	Gel Vehicle (ER/N)	P-value
Incidence of complete eschar removal	93.3% 70/75	4.0% (1/25)	p < 0.0001

ER= eschar removal

Compared to SOC, NexoBrid resulted in significant reductions in the incidence of surgical eschar removal (tangential/minor/avulsion/Versajet and/or dermabrasion excision), median time to complete eschar removal, and actual blood loss related to eschar removal as shown below.

Incidence of surgical eschar excision, time to complete eschar removal, and blood loss in the DETECT study

	NexoBrid (N=75)	Standard of Care (N=75)	P-value
Incidence of surgical excision (number of subjects)	4.0% (3)	72.0% (54)	p < 0.0001
Median time to complete eschar removal	1.0 days	3.8 days	p < 0.0001
Blood loss related to eschar removal[a]	14.2 ±512.4 mL	814.5 ±1020.3 mL	p < 0.0001

[a] Actual Blood Loss calculated using the method described in McCullough 2004:

$$ABL = \frac{EBV*(Hb_{before}-Hb_{after})}{(Hb_{before}+Hb_{after})/2} + V_{WB} + \frac{5}{3}V_{PC}$$

EBV= Estimated blood volume is assumed 70 cm^3/kg*weight (kg); (Hb_{before}- Hb_{after}) = Change in Hb during the eschar removal process; V_{WB}= Volume [mL] of whole blood transfused during the eschar removal process; V_{PC}= Volume [mL] of packed red blood cells transfused during the eschar removal process.

Study MW2004-11-02 (Phase 3)

This was a randomised, multi-centre, multi-national, open-label, confirmatory phase 3 study evaluating NexoBrid compared to SOC in hospitalised patients with deep partial- and/or full-thickness thermal burns of 5 to 30% TBSA, but with total burn wounds of no more than 30% TBSA.

Standard of care consisted of primary surgical excision and/or nonsurgical debridement using topical medicinal products to induce maceration and autolysis of eschar according to each study site's standard practice.

The age range in the group treated with NexoBrid was 4.4 to 55.7 years. The age range in the SOC group was 5.1 to 55.7 years.

The efficacy of eschar removal was evaluated by determining the percentage of wound area left with eschar that required further removal by excision or dermabrasion, and the percentage of wounds requiring such surgical removal.

The effect on the timing of eschar removal was evaluated in patients with successful eschar removal (with at least 90% eschar removal in all wounds of a patient combined), by determining the time from injury as well as from informed consent to successful removal.

The co-primary endpoints for the efficacy analysis were:

- the percentage of deep partial thickness wounds requiring excision or dermabrasion, and
- the percentage of deep partial thickness wounds autografted.

The second co-primary endpoint can only be evaluated for deep partial-thickness wounds without full-thickness areas because full-thickness burns always require grafting.

Efficacy data generated in this study for all age groups combined are summarised below.

	NexoBrid	SOC	p-value
Deep partial-thickness wounds requiring excision/dermabrasion (surgery)			
Number of wounds	106	88	
% of wounds requiring surgery	15.1%	62.5%	<0.0001
% of wound area excised or dermabraded[1] (mean ± SD)	5.5% ± 14.6	52.0% ± 44.5	<0.0001
Deep partial-thickness wounds autografted*			
Number of wounds	106	88	
% of wounds autografted	17.9%	34.1%	0.0099
% of wound area autografted (mean ± SD)	8.4% ± 21.3	21.5% ± 34.8	0.0054
Deep partial- and/or full-thickness wounds requiring excision/dermabrasion (surgery)			
Number of wounds	163	170	
% of wounds requiring surgery	24.5%	70.0%	<0.0001
% of wound area excised or dermabraded[1] (mean ± SD)	13.1% ± 26.9	56.7% ± 43.3	<0.0001
Time to complete wound closure (time from ICF)**			
Number of patients[2]	70	78	
Days to closure of last wound (mean ± SD)	36.2 ± 18.5	28.8 ± 15.6	0.0185
Time to successful eschar removal			
Number of patients	67	73	
Days (mean ± SD) from injury	2.2 ± 1.4	8.7 ± 5.7	<0.0001
Days (mean ± SD) from consent	0.8 ± 0.8	6.7 ± 5.8	<0.0001
Patients not reported to have successful eschar removal	7	8	

1 Measured at first session, if there was more than one surgery session.

2 All randomised patients for whom data for complete wound closure were available.

*The endpoint can only be evaluated for deep partial-thickness wounds without full-thickness areas because full-thickness burns always require grafting.

** Informed Consent Form

Analysis of wound-closure data

In the DETECT (2010 03-02) study, median time to complete wound closure estimated using the Kaplan Meyer method was 27 days and 28 days for the NexoBrid and SOC treatment arms, respectively. The p-value equals 0.0003, establishing non-inferiority (7 day non-inferiority margin) of NexoBrid treatment arm compared to SOC. Median time calculated using actual data was 23 days for the NexoBrid and SOC treatment arms. Results from pooled wound closure data from both phase 3 studies supported the non-inferiority of NexoBrid compared with SOC based on a 7-day non-inferiority margin. Based on pooled data from the DETECT study and study MW2004-11-02, time to complete wound closure was slightly longer in the NexoBrid group than in the SOC group, when estimated by the Kaplan-Meier method (median 30.0 days vs 25.0 days) or calculated using actual data (mean 31.7 days vs 29.8 days). According to the non-inferiority analysis, time to complete wound closure was less than 7 days longer with NexoBrid than with SOC (p for non-inferiority=0.0006).

Safety and efficacy in paediatric patients

The available data are limited and NexoBrid should not be used in patients younger than 18 years.

Long-term data

The Phase 3 trial (DETECT) included long-term follow up to assess cosmesis and function. At 12 months, scar assessment using the Modified Vancouver Scar Score (MVSS) demonstrated comparable outcomes between the NexoBrid, SOC, and Gel Vehicle arms, with mean scores of 3.70, 5.08, and 5.63, respectively. Statistical analyses indicated non-inferiority (pre-defined NI margin of 1.9 points) of NexoBrid treatment compared SOC ($p<0.0027$).
Functionality and quality of life measurements at 12 months were generally similar across treatment groups.

Pharmacokinetics

Absorption

Pharmacokinetic analyses were performed in a subset of NexoBrid patients who participated in study MW2008 09 03 and study MW2010-03-02 (DETECT), using the same bioanalytical method.
Following topical administration of NexoBrid, evidence of systemic serum exposure was observed in all patients. In general, NexoBrid appears to be rapidly absorbed, with a median t_{max} value of 4.0 hours (duration of treatment application). NexoBrid exposure was observed with quantifiable serum concentrations through 48 hours post dose administration. A majority of patients had no quantifiable concentrations after 72 hours.
Exposure results from MW2008-09-03 and MW2010-03-02 studies are listed below.
Within each study the C_{max} and the dose normalized C_{max} values after the first and second application are comparable. Comparison of the AUC_{0-4} and AUC_{0-4} dose normalized levels in the first application versus second application indicates that the exposure values are slightly higher after second application, but considered comparable (less than 2-fold). Not all patients had values beyond 4 hours, as such the AUC_{last} values for some patients only cover 4 hours of exposure versus 48 hours of exposure for other patients.
In both PK studies there was a statistically significant correlation between serum C_{max} and AUC_{0-4} values versus dose or %TBSA, suggesting a dose or treatment area dependent increase in exposure.
The depth of the NexoBrid treated-wound has negligible impact on systemic exposure.

Summary of PK parameters* measured in all patients from studies MW2008 and MW2010 (first application)

Study ID	N	T_{max} Median (range) (h)	C_{max} (ng/mL)	C_{max}/Dose (ng/mL/g)	AUC_{0-4} (h*ng/mL)	AUC_{0-4}/Dose (h*ng/mL/g)	AUC_{last} (h*ng/mL)	AUC_{last}/Dose (h*ng/mL/g)
Study MW2008-09-03								
	13[a]	4.0 (0.50 - 4.1)	800±640 (Min=222) (Max=2440)	44.7±36.6	1930±648	103±48.8	2760±2870	149±147
Study MW2010-03-02								
	21	4.0 (0.50 – 12)	200±184 (Min=30.7) (Max=830)	16.4±11.9	516±546	39.8±29.7	2500±2330	215±202

*Values are reported as Mean ± SD, which the exception of T_{max}, which is reported as Median (Min-Max).

[a] n=8 for AUC_{0-4h} and $AUC_{0-4h/dose}$

AUC_{last}=area under the curve until last measurable time-point, AUC_{0-4}=area under the concentration-time curve from time zero to time 4h, C_{max}=maximum observed concentration, T_{max}=time at which the maximum concentration was observed

Distribution

According to a literature report, in plasma, approximately 50% of bromelain binds to the human plasma antiproteinases α2-macroglobulin and α1-antichymotrypsin.

Metabolism

Elimination

The median terminal half-life in Study MW2008-09-03 was 12 ± 4.4 hours.

Kinetics in specific patient groups

Children and adolescents

Pharmacokinetic parameters and the extent of absorption have not been studied in children.

Preclinical data

Repeat dose toxicity

A single intravenous infusion of a solution prepared from NexoBrid powder in the mini-pig was well tolerated at dose levels of up to 12 mg/kg (achieving plasma levels 2.5 fold of the human plasma level after application of the clinical proposed dosage to 15% TBSA) but higher doses were overtly toxic, causing haemorrhage in several tissues. Repeated intravenous injections of doses up to 12 mg/kg every third day in the mini-pig were well tolerated for the first three injections but severe clinical signs of toxicity (e.g. haemorrhages in several organs) were observed following the remaining three injections. Such effects could still be seen after the recovery period of 2 weeks.

Mutagenicity

NexoBrid showed no genotoxic activity when investigated in the standard set of *in vitro* (reverse Mutation Assay Using Bacteria S. typhimurium, *in vitro* Mammalian Chromosome Aberration Test in Chinese Hamster V79 Cells) and *in vivo* (Mammalian Micronucleus Test of Murine Bone Marrow Cells) studies.

Carcinogenicity

Carcinogenicity studies have not been conducted with NexoBrid.

Developmental toxicity

In embryo-foetal development studies in rats and rabbits, intravenously administered NexoBrid revealed no evidence of indirect and direct toxicity to the developing embryo/foetus. However, maternal exposure levels were considerably lower than those maximally reported in clinical setting (10–500 times lower than human AUC, 3–50 times lower than the human C_{max}). Since NexoBrid was poorly tolerated by the parent animals, these studies are not considered relevant for human risk assessment.

Local toxicity

NexoBrid was well tolerated when applied to intact mini-pig skin but caused severe irritation and pain when applied to damaged (abraded) skin.

Other information

Incompatibilities

Topically applied medicinal products (such as silver sulfadiazine or povidone-iodine) at the wound site must be removed and the wound cleansed prior to NexoBrid application. Remaining antibacterial medicinal products may interfere with the activity of NexoBrid by decreasing its efficacy.
This medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.
From a microbiological point of view and as the enzymatic activity of the product decreases progressively following mixing, the reconstituted product should be used immediately after preparation (within 15 minutes).

Special precautions for storage

Store and transport refrigerated (2°C - 8°C).
Store upright to keep the gel at the bottom of the bottle and in the original package to protect from light.
Do not freeze.
Keep out of the reach of children.

Instructions for handling

There are reports of occupational exposure to bromelain leading to sensitisation. Sensitisation may have occurred due to inhalation of bromelain powder. Allergic reactions to bromelain include anaphylactic reactions and other immediate-type reactions with manifestations such as bronchospasm, angiooedema, urticaria, and mucosal and gastrointestinal reactions. This should be considered when mixing NexoBrid powder with the gel. The powder should not be inhaled. See also section “Warnings and precautions”.
Accidental eye exposure must be avoided. In case of eye exposure, exposed eyes must be irrigated with copious amounts of water for at least 15 minutes. In case of skin exposure, NexoBrid must be rinsed off with water.
NexoBrid gel preparation (mixing powder with gel)

- The NexoBrid powder and gel are sterile. An aseptic technique must be used when mixing the powder with the gel.
- The powder vial must be opened by carefully tearing off the aluminium cap and removing the rubber stopper. The powder should not be inhaled. Appropriate handling of the debriding agent (including wearing of gloves and protective clothing as well as a surgical mask) is mandatory.
- When opening the gel bottle, it must be confirmed that the tamper-evident ring is separating from the bottle’s cap. If the tamper-evident ring was already separated from the cap before opening, the gel bottle must be discarded and another, new gel bottle used.
- The powder is then transferred into the corresponding gel bottle.
- Powder and gel must be mixed thoroughly until a uniform, slightly tan to slightly brown mixture is obtained. This usually requires mixing the powder and the gel for 1 to 2 minutes.
- The gel should be prepared at the patient’s bedside.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68012 (Swissmedic)

Packs

Pack size of 1 vial of powder and 1 bottle of gel.
NexoBrid 5 g [A]

Marketing authorisation holder

Triskel Integrated Services, Le Grand-Saconnex-Geneva

Date of revision of the text

Décembre 2021