נקסובריד 2 ג' 5 ג'

Eng **Package leaflet:**
Information for the user

Package leaflet: Information for the user

NexoBrid 2 g powder and gel for gel /
NexoBrid 5 g powder and gel for gel
concentrate of proteolytic enzymes enriched in bromelain

1. NAME OF THE MEDICINAL PRODUCT

NexoBrid 2 g powder and gel for gel/ NexoBrid 5 g powder and gel for gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 2 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 2 g/22 g gel).
One vial 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).

The proteolytic enzymes are a mixture of enzymes from the stem of Ananas comosus (pineapple plant).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and gel for gel.
The powder is off-white to light tan. The gel is clear and colourless.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

This medicinal product should only be applied by trained healthcare professionals in specialist burn centres.

Posology
2g powder in 20 g gel is applied to a burn wound area of 1 % Total Body Surface Area (TBSA) of an adult, with a gel layer thickness of 1.5 to 3 mm.
5g 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.

The gel should not be applied to more than 15% TBSA (see also section 4.4, Coagulopathy).

It should be left in contact with the burn for a duration of 4 hours. There is very limited information on the use of this medicinal product on areas where eschar remained after the first application. A second and subsequent application is not recommended.

Special populations

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

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

Elderly patients
Experience in elderly patients (>65 years) is limited. No dose adjustment is required.

Paediatric population
The safety and efficacy of this treatment in children and adolescents younger than 18 years have not yet been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.
This medicinal product is not indicated for use in patients younger than 18 years.

Method of administration
Cutaneous use.
Before use, the powder must be mixed with the gel producing a uniform gel (For instructions on mixing see section 6.6).
Once mixed, the gel should be applied to a clean, keratin-free (blisters removed), and moist wound area.
Each vial, gel, or reconstituted gel should be used for a single use only.
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 application of the gel as eschar saturated with medicinal products and their remains reduce its activity and decrease its efficacy.
For instructions on preparation of the medicinal product before application, see section 6.6.

Precaution to be taken before manipulating or administering the product
When mixing this medicinal product powder with the gel, appropriate handling, including wearing of gloves and protective clothing as well as eye shielding glasses and a surgical mask, is required (see section 4.4). The powder should not be inhaled, see section 6.6.

Preparation of patient and wound area
A total wound area of not more than 15% TBSA can be treated with this medicinal product (see also section 4.4, Coagulopathy).
- Enzymatic debridement is a painful procedure and requires adequate analgesia and/or anaesthesia. 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 the gel and prevent eschar removal by it.
- Dressing soaked with an antibacterial solution must be applied for 2 hours.
- All topically applied antibacterial medicinal products must be removed before applying the gel. Remaining antibacterial medicinal products may reduce 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 the gel. To prevent possible irritation of abraded skin by inadvertent contact with the gel 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.

Application of the gel
- Moisten the area to be treated by sprinkling sterile saline onto the area bordered by the fatty ointment adhesive barrier.
- Within 15 minutes of mixing, the gel 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 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 the gel 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 the gel
- Removal of this medicinal product is a painful procedure and requires adequate analgesia and/or anaesthesia. Appropriate preventive analgesia medicinal products must be administered at least 15 minutes prior to gel application.
- After 4 hours of this medicinal product 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 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 the treatment debridement. Careful consideration should also be given to placing permanent skin covers (e.g. autografts) on deep partial thickness wounds soon after the treatment debridement. (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance, to pineapples, or papain (see also section 4.4), or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

Hypersensitivity reactions
The potential of this medicinal product (a protein product) to cause sensitisation should be taken into account.
There have been reports of serious allergic reactions including anaphylaxis (with manifestations such as rash, erythema, hypotension, tachycardia) in patients undergoing debridement with the treatment (see section 4.8). In these cases, a causal relationship to this medicinal product was considered possible, but possible allergy to concomitant medicinal products such as opioid analgesics should also be considered.
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. In addition, a delayed-type allergic skin reaction (cheilitis) after longer-term dermal exposure (mouthwash) as well as suspected sensitisation following oral exposure and following repeated occupational airway exposure have been reported.
History of allergy needs to be established prior to the administration (see sections 4.3 and 6.6).

Skin exposure
In case of skin exposure, this medicinal product should be rinsed off with water to reduce the likelihood of skin sensitisation (see section 6.6).

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.

Analgesia
Enzymatic debridement is a painful procedure, and may only be administered after adequate analgesia and/or anesthesia has been established.
Burn wounds for which this medicinal product is not recommended
This treatment 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.
- wounds contaminated with radioactive and other hazardous substances to avoid unforeseeable reactions with the product and an increased risk of spreading the noxious substance.
- foot burns in diabetic patients and patients with occlusive vascular disease
- in electrical burns.

Burns for which there is limited or no experience
There is no experience of the use of medicinal product on perineal and genital burns:
- perineal and genital burns.

Use in patients with cardiopulmonary and pulmonary disease
This medicinal product should be used with caution in patients with cardiopulmonary and pulmonary disease, including pulmonary burn trauma and suspected pulmonary burn trauma.

Facial burn wounds
There are literature reports of successful use of this medicinal product on facial burn wounds. Burn surgeons without experience in using this medicinal product should not start using it on facial burn wounds. The treatment must be used with caution in such patients.

Eye protection
Direct contact with the eyes must be avoided. Eyes must 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.
In case of eye exposure, irrigate exposed eyes with copious amounts of water for at least 15 minutes. An ophthalmological exam is recommended prior to and after debridement.

Systemic absorption
Concentrate of proteolytic enzymes enriched in bromelain is systemically absorbed from burn wound areas (see section 5.2).
There is limited pharmacokinetic data in patients with TBSA of more than 15%. Due to safety considerations (see also section 4.4, Coagulopathy) this medicinal product should not be applied to more than 15%Total Body Surface Area (TBSA).

Prevention of wound complications
General principles of proper burn wound care must be adhered to when using this medicinal product. This includes proper wound cover for the exposed tissue (see section 4.2).
In clinical 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 that will not heal spontaneously by epithelialisation in timely manner should be autografted as soon as possible after NexoBrid debridement (see section 5.1). Careful consideration should also be given to placing permanent skin covers (e.g. autografts) on deep partial thickness wounds soon after NexoBrid debridement. (see sections 4.2 and 4.8).
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.

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 this medicinal product, there was no indication of an increased bleeding tendency or bleeding at the site of debridement.
The treatment should not be used in patients with uncontrolled disorders of coagulation. It should be used with caution in patients under anticoagulant therapy or other medicinal products affecting coagulation, and in patients with 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.

Clinical 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 this medicinal product 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 this medicinal product. Remaining antibacterial medicinal products reduce the activity of this medicinal product by decreasing its efficacy.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Medicinal products that affect coagulation
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 4.4.)

CYP2C8 and CYP 2C9 substrates
The medicinal product, when absorbed, is an inhibitor of cytochrome P450 2C8 (CYP2C8) and P450 2C9 (CYP2C9). This should be taken into account if this medicinal product is used in patients receiving CYP2C8 substrates (including amiodarone, amodiaquine, chloroquine, fluvastatin, paclitaxel, pioglitazone, repaglinide, rosiglitazone, sorafenib and torasemide) and CYP2C9 substrates (including ibuprofen, tolbutamide, glipizide, losartan, celecoxib, warfarin, and phenytoin).

Topical antibacterial medicinal products
Topically applied antibacterial medicinal products (e.g. silver sulfadiazine or povidone iodine) may decrease the efficacy of this medicinal product (see section 4.4).

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

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

Benzodiazepines, barbiturates, narcotics and antidepressants
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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of concentrate of proteolytic enzymes enriched in bromelain in pregnant women.
Animal studies are insufficient to properly assess the potential of this medicinal product to interfere with embryonal/foetal development (see section 5.3).

Since the safe use of medicinal product during pregnancy has not yet been established, it is not recommended during pregnancy.

Breastfeeding
It is unknown whether concentrate of proteolytic enzymes enriched in bromelain or its metabolites are excreted in human milk. A risk to new-borns/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 this medicinal product on fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions are transient pyrexia/hyperthermia and local pain (incidence of 15.2 % and 4.0% respectively)

Tabulated list of adverse reactions
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 this medicinal product 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 the treatment for 4 hours with an occlusive dressing for containment of NexoBrid on the wound.

Infections and infestations
Common: Wound infection*

Immune system disorders
Common: Non serious allergic reactions such as rash[a]
Not known: Serious allergic reactions including anaphylaxis[a]

Cardiac disorders
Common: Tachycardia*

Skin and subcutaneous tissue disorders
Common: Wound complication*

General disorders and administration site conditions
Very common: Pyrexia/hyperthermia*
Common: Local pain*

*see Description of selected adverse reactions below.
[a] see section 4.4.

Description of selected adverse reactions

Pyrexia/hyperthermia
In pooled studies MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02 with routine antibacterial soaking of the treatment area before and after this medicinal product application (see section 4.2) pyrexia or hyperthermia was reported in 15.2% of patients treated with it and in 11.3% of the control patients treated according to standard of care (SOC).
In early studies without antibacterial soaking (Studies MW2001-10-03 and MW2002-04-01), pyrexia or hyperthermia was reported in 35.1% of NexoBrid-treated patients compared with 8.6% treated with SOC.

Local pain
In pooled studies MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02 where the medicinal product regimen included recommended preventive analgesia as routinely practiced for extensive dressing changes in burn patients (see section 4.2), pain was reported in 4.0% of patients treated with medicinal product, and in 3.8% of the control patients treated according to SOC.
In early studies where analgesia was provided in medicinal

13/04/03V1222

product-treated patients on an on-demand basis, pain was reported in 23.4% of patients treated with medicinal product and in 5.7% in the SOC group.

Wound infection
In pooled studies with routine antibacterial soaking of the treatment area before and after medicinal product application (studies MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02 studies), the incidence of wound infection was 5.4% in the medicinal product group and 8.1% in the standard of care group.
In pooled studies which were conducted before implementation of routine antibacterial soaking of the treatment area (studies MW2001-10-03 and MW2002-04-01), The incidence of wound infection was 7.8% in the medicinal product group and 0% in the standard of care group

Wound complications
Wound complications reported include the following: wound deepening, wound desiccation, wound re-opening, graft loss/ graft failure, and local intradermal haematoma.
In pooled phase 2 and 3 studies (MW2001-10-03, MW2002-04-01, MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02) including 300 patients treated with NexoBrid and 195 patients treated with SOC, the following incidence was reported: wound complication 3% in the NexoBrid treated patients and 1.5% in patients treated with SOC, skin graft loss/ graft failure 3% in the patients treated with NexoBrid and in 2.5% in patients treated with SOC, wound decomposition 1% in both the NexoBrid and SOC treated patients, local intradermal hematoma 0.7% in NexoBrid treated patients and none in the SOC treated patients.

Tachycardia
In pooled phase 2 and 3 studies (MW2001-10-03, MW2002-04-01, MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02) 2.7% of patients experienced tachycardia in temporal proximity to NexoBrid treatment. Alternative causes of tachycardia (e.g. the general burn condition, procedures causing pain, fever and dehydration) should be considered.

Paediatric population
There is only limited safety data from the use in the paediatric population. From these data it is expected that the overall safety profile in children 4 years of age and older and in adolescents is similar to the profile in adults. This medicinal product is not indicated for use in patients younger than 18 years (see section 4.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose
Treatment with concentrate of proteolytic enzymes enriched in bromelain prepared in a powder:gel ratio of 1:5 (0.16g 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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Preparations for treatment of wounds and ulcers, proteolytic enzymes; ATC code: **D03BA03**.

Mechanism of action
The mixture of enzymes in this medicinal product dissolves burn wound eschar. The specific components responsible for this effect have not been identified. The major constituent is stem bromelain.

Clinical efficacy and safety
During clinical development, a total of 467 patients were treated with the concentrate of proteolytic enzymes enriched in bromelain.

DETECT study (MW2010-03-02)- (Phase 3b)
This study is a multi-center, multi-national, assessor-blinded, randomised, controlled, three-arm study aimed at demonstrating superiority of this medicinal product treatment over Gel Vehicle (placebo) control and standard of care (SOC) treatment, in hospitalised adult subjects with DPT and/or FT thermal burn of >3% TBSA and total burn wounds of no more than 30% TBSA. The mean % TBSA of Target Wound TWs was about 6%.

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 12 months follow-up visit.

A total of 175 subjects were randomised (Intend to Treat cohort) in a 3:3:1 ratio (medicinal product:SOC: Gel Vehicle), and 169 subjects were treated. Patients in the SOC treatment arm were treated with surgical and/or non-surgical 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 this medicinal product was 18 to 75 years, 18 to 72 years in the SOC group and 18 to 70 years in the Gel Vehicle group. Sixteen patients ≥ 65 years old (9,1%) were included in the study. Seven (7) (9.3%) patients in the medicinal product arm, 5 (6.7%) patients in the SOC arm, and 4 (16%) patients in the gel vehicle arm. Mean age in all 3 arms was 41 years, and 65%, 79%, and 60% of subjects were male in the medicinal product, 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 medicinal product 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.

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, the medicinal product resulted in significant reductions in the incidence of surgical eschar removal (tangential/ minor/avulsion/Versajet and/or dermabrasion excision), time to complete eschar removal, and actual blood loss related to eschar removal, as shown below. Similar efficacy of eschar removal was observed in the elderly population.

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 removala	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:

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

EBV= Estimated blood volume is assumed 70 cm3/kg*weight (kg); (Hbbefore- Hbafter) = Change in Hb during the eschar removal process; V_{WB}= Volume [mL] of whole blood transfused during the eschar removal process; V_{RC}= Volume [mL] of packed red blood cells transfused during the eschar removal process.

Long-term data (12 months)
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 medicinal product, SOC, and Gel Vehicle, 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 the medicinal product treatment compared to SOC (p<0.0027).

Functionality and quality of life (QOL) measurements at 12 months were similar across treatment groups. The mean Lower Extremity Functional Scale (LEFS) scores were similar between the medicinal product and SOC (and slightly lower with Gel Vehicle). The mean QuickDASH scores were similar between SOC and Gel Vehicle and slightly lower with the medicinal product. The results of range of motion (ROM) evaluations were similar for the medicinal product and SOC, with a higher percentage of patients with abnormal ROM scores in the Gel Vehicle group. Long-term QOL, as measured by EQ-5D VAS (visual analogue scale) and Burn Specific Health Scale-Brief (BSHS-B), was similar among treatment arms.

Cardiac safety:
In a cardiac safety sub study, the ECGs of up to 150 patients were used to evaluate potential effects of this medicinal product on ECG parameters. The study showed no clear effect of this medicinal product on heart rate, PR interval, QRS duration (cardiac depolarisation), and cardiac repolarisation (QTc). There were no new clinically relevant morphological ECG changes demonstrating a signal of concern

Study MW2004-02-11 (Phase 3)
This was a randomised, multi-centre, multi-national, open-label, confirmatory phase 3 study evaluating this medicinal product 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. The mean TW area treated in % TBSA was 5.1±3.5 for this medicinal product and 5.2±3.4 for SOC.

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 this medicinal product 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 as well as from a subgroup analysis for children and adolescents 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

Long-term data
A multi-center, non-interventional, assessor-blinded study (MW2012-01-02) evaluated the long-term scar formation and quality of life in adults and children who participated in study MW2004-11-02.
A total of 89 subjects were enrolled into the study including 72 adults (>18) and 17 pediatric subjects. Comparison of baseline characteristics between subjects enrolled into MW2012-01-02 and non-enrolled subjects indicated that the enrolled population is representative of the MW-2004-11-02 study population.
Scar assessment at 2-5 years using the MVSS demonstrated comparable outcomes between study groups with the mean total overall score of 3.12 and 3.38 for the medicinal product and SOC, respectively (p=0.88).
QOL was assessed in adults using the SF-36 questionnaire. Mean scores for the various parameters were similar in the medicinal product compared to SOC group. The overall physical component score (51.1 and 51.3, respectively) and the overall mental component score (51.8 vs. 49.1, respectively) were comparable between the medicinal product and SOC groups.

Paediatric population
Efficacy data generated in study MW2004-11-02 from a subgroup analysis for children and adolescents are summarised below. The available data are limited and this medicinal product should not be used in patients younger than 18 years.

	NexoBrid	SOC	p-value
Deep partial-thickness wounds requiring excision/dermabrasion (surgery)			
Number of wounds	23	22	
% of wounds requiring surgery	21.7%	68.2%	0.0017
% of wound area excised or dermabraded[1] (mean ± SD)	7.3% ± 15.7%	64.9% ± 46.4%	<0.0001
Deep partial-thickness wounds autografted*			
Number of wounds	23	22	
% of wounds autografted	21.7%	31.8%	0.4447
% of wound area autografted (mean ± SD)	6.1% ± 14.7%	24.5% ± 40.6%	0.0754
Deep partial- and/or full-thickness wounds requiring excision/dermabrasion (surgery)			
Number of wounds	29	41	
% of wounds requiring surgery	20.7%	78%	<0.0001
% of wound area excised or dermabraded[1] (mean ± SD)	7.9% ± 17.6%	73.3% ± 41.1%	<0.0001
Time to complete wound closure (time from ICF)**			
Number of patients[2]	14	15	
Days to closure of last wound (mean ± SD)	29.9 ± 14.3	32.1 ± 18.9	0.6075
Time to successful eschar removal			
Number of patients	14	15	
Days (mean ± SD) from injury	1.9 ± 0.8	8.1 ± 6.3	<0.0001
Days (mean ± SD) from consent	0.9 ± 0.7	6.5 ± 5.9	<0.0001
Patients not reported to have successful eschar removal	0	1	

[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

The European Medicines Agency has deferred the obligation to submit the results of studies with this medicinal product in one or more subsets of the paediatric population in the treatment of burns of external body surface (see section 4.2 for information on paediatric use).

Pooled phase 3 studies (studies MW2010-03-02 and MW2004-02-11)

Analysis of wound-closure data
In the DETECT (MW2010 03-02) study, measured mean time to complete wound closure was 29.35 days [SD 19.33] and 27.77 days [SD 19.83] SOC for the medicinal product and SOC treatment arms, respectively (estimated median time: 27 days medicinal product vs. 28 days SOC Non-inferiority = (7 day non-inferiority margin) of NexoBrid treatment arm compared to SOC was established (p=0.0003).
Results from pooled wound closure data from both phase 3 studies supported the non-inferiority of the medicinal product compared with SOC based on a 7-day non-inferiority margin. Based on pooled data from the DETECT study and study MW2004-02-11, time to complete wound closure was slightly longer in the medicinal product group than in the SOC group, when calculated using actual data (mean 31.7 days medicinal product vs 29.8 days SOC) or estimated by the Kaplan-Meier method (median 30.0 days vs 25.0 days). Time to complete wound closure was less than 7 days longer with this medicinal product than with SOC (p for non-inferiority=0.0006).

Serious adverse events:
Pooled analysis from phase 3 studies (studies MW2010-03-02 and MW2004-02-11 showed that the percentages of patients who experienced serious TEAEs were similar (<2% difference) in the medicinal product (8.5%; 15/177) and SOC (6.7%; 10/149) groups.
Serious TEAEs were most frequently reported within the system organ class of Infections and Infestations for both the medicinal product (2.8%) and SOC (2.7%) groups.
Only 2 events occurred in more than 1 patient (sepsis occurred in 3 patients in the medicinal product group and 1 patient in the SOC group, bacterial wound infection occurred in 2 patients in the medicinal product group and wound infection occurred in one patient in the SOC group).

Sepsis and bacteraemia related adverse events (serious and non-serious) were reported in similar incidence rate in medicinal product and SOC groups: 2.8% in the medicinal product and 2% in the SOC group.

5.2 Pharmacokinetic properties

Absorption
Exploratory 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. The analyses were performed on serum NexoBrid concentration versus time data and number of treatment applications.

Following topical administration of this medicinal product, evidence of systemic serum exposure was observed in all patients. In general, it 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. When evaluated, a majority of patients had no quantifiable concentrations after 72 hours.

Exposure results from MW2008-09-03 and MW2010-03-02 studies are listed in the table below.
Not all patients had values beyond 4 hours, as such the AUClast 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 Cmax and AUC_{0-4} values versus dose or %TBSA, suggesting a dose / treatment area dependent increase in exposure. The depth of the medicinal product treated-wound has negligible impact on systemic exposure.

Summary of PK parameters* measured in all patients from studies MW2008-09-03 and MW2010-03-02

Study ID	N	T_{max} Median (range) [h]	C_{max} (ng/mL)	C***/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	4.0 (0.50 - 4.1)	800±640	44.7±36.6	1930±648a	103±48.8a	2760±2870	149±147
Study MW2010-03-02								
	21	4.0 (0.50 - 12)	200±184 (Min=30.7 (Max=826)	16.4±11.9	516±546	39.8±29.7	2500±2330	215±202

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

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.

Elimination
The mean elimination half-life values ranged between 12 and 17 hours, supporting the decreased presence of medicinal product in serum at 72 hours post treatment.

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

5.3 Preclinical safety data
This medicinal product did not cause significant irritation when applied to intact mini-pig skin but caused severe irritation and pain when applied to damaged (abraded) skin.

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 2.5fold of the human plasma level after application of the clinical proposed dose 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.

In embryo-foetal development studies in rats and rabbits, intravenously administered medicinal product 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 Cmax). Since this medicinal product was poorly tolerated by the parent animals, these studies are not considered relevant for human risk assessment. NexoBrid showed no genotoxic activity when investigated in the standard set of in vitro and in vivo studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Powder
Ammonium sulphate
Acetic acid

Gel
Carbomer 980
disodium phosphate anhydrous
Sodium hydroxide
Water for injections

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products. except those mentioned in section 6.6.

6.3 Shelf life
3 years.

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).

6.4 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.

6.5 Nature and contents of container
2 g powder in a vial (glass type II) sealed with a rubber (bromobutyl), stopper and covered with a cap (aluminium), and 20 g gel in a bottle (borosilicate, glass type I), sealed with a rubber stopper and covered with a screw cap (tamper-proof polypropylene).
5 g powder in a vial (glass type II) sealed with a rubber (bromobutyl), stopper and covered with a cap (aluminium), and 50 g gel in a bottle (borosilicate, glass type I), sealed with a rubber stopper and covered with a screw cap (tamper-proof polypropylene).

Pack size of 1 vial of powder and 1 bottle of gel.

6.6 Special precautions for disposal and other 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. When mixing this medicinal product powder with the gel, appropriate handling, including wearing of gloves and protective clothing as well as eye shielding glasses and a surgical mask, is required (see section 4.4). The powder should not be inhaled. See section 4.2.

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, this medicinal product must be rinsed off with water.

Gel (mixing powder with gel)
- The 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.
- 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.

7. MARKETING AUTHORISATION HOLDER
MediWound Ltd.
42 Hayarkon Street,
Yavne 8122745
Israel

Revised in December 2022 according to MOHs guidelines