ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NexoBrid 5 g powder and gel for gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 5g of concentrate of proteolytic enzymes enriched in bromelain, corresponding to 0.09 g/g concentrate of proteolytic enzymes enriched in bromelain after mixing (5g/55g 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 in all age groups for removal of eschar in patients 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

Adults
5g powder in 50 g gel is applied to 2.5 % Total Body Surface Area (TBSA) that corresponds to approximately 450 cm^2 of an adult, with a gel layer thickness of 1.5 to 3 mm.

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

Paediatric population
Children and adolescents (from birth to 18 years of age)
For paediatric patients aged 4-18 years old NexoBrid should not be applied to more than 15% TBSA.
For paediatric patients aged 0-3 years old this medicine should not be applied to more than 10% TBSA.

It should be left in contact with the burn wound 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.

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 this medicinal product 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 this medicinal product 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 medicinal product

- 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 *medicinal product* 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 medicinal product
- 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 removal.
- After 4 hours of 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 debridement. Careful consideration should also be given to placing permanent skin covers (e.g. autografts) on deep partial thickness wounds soon after the debridement (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance, to pineapples, or papayas/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 this medicinal product (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 this medicinal product 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 papaya/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 this medicinal product on 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.

Use in patients with varicose veins

This medicinal product should be used with caution in areas of varicose veins, to prevent erosion of the veins' wall, and the risk of bleeding.

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. This medicinal product 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) in adults and paediatric patients aged 4-18 years old.

For paediatric patients aged 0-3 years old this medicinal product should not be applied to more than 10% 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 this medicinal product 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 this medicinal product 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 this medicinal product 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, , 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.

Paediatric population

No interaction studies have been performed in children/adolescents.

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 in pooled adult population from studies MW2004, MW2005, MW2008 and MW2010 in the medicinal product arm (203 patients in total) are pyrexia and pain (incidence of 13.3 and 3.9%, respectively).

The most commonly reported adverse reactions in the pooled paediatric population (0-18 years) (89 patients in total) from studies, MW2004, MW2008 and MW2012 in the medicinal product arm were pyrexia and pain (incidence of 16.9% and 7.9%, respectively).

Tabulated list of adverse reactions up to 3 months post wound closure

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/anaesthesia, as well as coverage of the wound area after application of the treatment for 4 hours with an occlusive dressing for containment of this medicinal product on the wound.

Infections and infestations
Common: Wound infection including cellulitis*

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 complications*, local rash, local pruritus,
Uncommon: intradermal haematoma

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 adult population from studies MW2004, MW2005, MW2008 and MW2010 with routine antibacterial soaking of the treatment area before and after this medicinal product application (see section 4.2), pyrexia hyperthermia and increased body temperature were reported in 13.3.% of the adult patients treated with this medicinal product vs. 9.7%, of the patients treated according to standard of care (SOC).
In early studies without antibacterial soaking (Studies MW2001and MW2002), pyrexia or hyperthermia was reported in (this medicinal product vs. SOC): 35.1% vs. 8.6% of adult patients.
In pooled paediatric population from studies MW2004, MW2008, and MW2012, with routine antibacterial soaking before and after treatment, fever-pyrexia or hyperthermia were reported in 16.9% of patients treated with this medicinal product vs. 9.3% of patients treated according to SOC.

Local pain
In pooled adults patients from studies MW2004, MW2005, MW2008 and MW2010 where preventive analgesia was practiced (as specified in section 4.2), pain related AEs were reported in 3.9% of -patients treated with this medicinal product vs. 3.5% of SOC-patients.
In early studies before implementation of the preventive actions (Studies MW2001 and MW2002) including adult patients, where analgesia was provided on an on-demand basis, pain was reported in 23.4% of patients treated with this medicinal product and in 5.7% in the SOC group.
In pooled paediatric population from studies MW2004, MW2008, and MW2012 (after implementation of preventive actions), pain was reported in (treated with this medicinal product vs. SOC): 7.9% vs. 9.3% of patients.

Wound infection
In pooled adult studies with routine antibacterial soaking of the treatment area before and after medicinal product application (studies MW2004, MW2005, MW2008 and MW2010), the incidence of wound infection was higher in the SOC group: 5.9% in the medicinal product group vs. 6.3% in the SOC group, and the incidence of cellulitis was 1.1% vs. 0.6% in medicinal product vs. SOC, respectively.
In pooled paediatric population from studies 2004, MW2008, and MW2012, wound infection were reported in 1.1% of this medicinal product patients vs. 8.1% of SOC-patients.

Wound complications
Wound complications reported include the following: wound deepening, wound desiccation, wound re-opening, graft loss/ graft failure.
In pooled adult populations from phase 2 and 3 studies including studies pre- and post-implementation of antibacterial soaking (MW2001, MW2002, MW2004, MW2005, MW2008, and MW2010) including 280 patients treated with this medicinal product and 179 patients treated with SOC, the following incidences were reported (medicinal product vs. SOC): wound complication: 3.2% vs. 1.7%, wound decomposition: 1.1% vs. 0.6%, skin graft failure/graft loss 2.9% vs 2.2% .

In pooled paediatric only population from studies MW2004, MW2008, and MW2012, wound complication was reported with similar incidence (medicinal product vs. SOC): 5.6% vs. 5.8%, skin graft failure/graft loss in this medicinal product vs SOC: 1.1% vs. 2.4%.

Tachycardia
In pooled adult population from phase 2 and 3 studies (MW2001, MW2002, MW2004, MW2005, MW2008 and MW2010), 2.9% of patients experienced tachycardia in temporal proximity to this medicinal product treatment. No tachycardia was reported in the SOC and gel vehicle arms.
In pooled paediatric population from studies MW2004, MW2008, and MW2012, tachycardia was reported with lower incidence in the medicinal product treated patients (1.1 %) compared SOC treated patients (3.5%).
Alternative causes of tachycardia (e.g., the general burn condition, procedures causing pain, fever and dehydration) should be considered.

Paediatric population

Clinical trial experience in paediatric patients (newborn up to 18 years of age) includes use of this medicinal product in a dedicated SOC-controlled study (MW2012), in which 69 patients were exposed to this medicinal product (age range new born-18 years; see section 5.1 for age distribution) and use in paediatric patients in studies MW2004 and MW2008, which included 17 and 3 paediatric patients, respectively (age range 4-17 years).
Overall, the safety profile in paediatric patients is similar to the safety profile in adults.
Due to the low numbers of adverse reactions reported in each age group, it is not possible to draw valid conclusions regarding potential age-related differences in the safety profile.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 536 patients were treated with the concentrate of proteolytic enzymes enriched in bromelain.

DETECT study (MW2010) - (Phase 3b)
This was a randomized, controlled, assessor-blinded, three-arm study comparing this medicinal product, standard of care (SOC), and gel vehicle treatment in adult subjects with DPT and/or FT thermal burns. SOC included both surgical and non-surgical methods for eschar removal per the investigators' discretion. Subjects on the medicinal product and gel vehicle arms who had eschar remaining following the topical treatment period were treated with SOC.

A total of 175 subjects were randomized in a 3:3:1 ratio (this medicinal product: SOC : gel vehicle) and 169 subjects were treated. The mean age was 41 years, 70% of subjects were male and 30% were female.

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. Subjects had one or more target wounds (TWs) to be treated for eschar removal. The mean percentage BSA of all TWs per subject was 6.1%. The majority of subjects (82%) had one to two TWs.

Primary endpoint was incidence of complete (>95%) eschar removal as compared with Gel Vehicle. Secondary endpoints included time to complete eschar removal, Incidence of surgical excision, 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, this 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)**
Incidence of surgical excision (number of subjects)	4.0% (3)	72.0% (54)
Median time to complete eschar removal	1.0 days	3.8 days
Blood loss related to eschar removal	14.2 ±512.4 mL	814.5 ±1020.3 mL

Long-term data (12 and 24 months after wound closure)

The Phase 3 trial (DETECT) included long-term follow up to assess cosmesis and function at 12 and 24 month follow up visits. At 12 months, scar assessment using the Modified Vancouver Scar Score (MVSS) demonstrated comparable outcomes between this medicinal product, SOC, and Gel Vehicle, with mean scores of 3.70, 5.08, and 5.63, respectively. At 24 months, MVSS mean scores were 3.04, 3.30 and 2.93 respectively. Statistical analyses indicated non-inferiority (pre-defined NI margin of 1.9 points) of this medicinal product treatment compared to SOC and showed that treatment with this medicinal product does not have any clinically meaningful deleterious effect on burn scar cosmesis and function compared with the SOC treatment at 24 months after wound closure.

Functionality and quality of life (QOL) measurements at 12 and 24 months were similar across treatment groups. The mean Lower Extremity Functional Scale (LEFS) scores, the mean QuickDASH scores, the range of motion (ROM) evaluations as well as long-term QOL, as measured by EQ-5D VAS (visual analogue scale) and Burn Specific Health Scale-Brief (BSHS-B) were 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 (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.
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 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	
Time to successful eschar removal			
Number of patients	67	73	
Days (mean ± SD) from consent	0.8 ± 0.8	6.7 ± 5.8	

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

The long-term scar formation and quality of life in adults and children who participated in study MW2004 were evaluated in a non-interventional, assessor-blinded extension study to MW2004.
The enrolled population of 89 subjects including 72 adults and 17 paediatric subjects (<18 years) was representative of the MW2004 study population.
Scar assessment at 2-5 years using the MVSS demonstrated comparable outcomes between study groups with a mean total overall score of 3.12 vs. 3.38 for the medicinal product vs. SOC, respectively (p=0.88).
QOL was assessed in adults using the SF-36 questionnaire. Mean scores for the various parameters were similar in both groups. The overall physical component score (51.1 vs. 51.3, respectively) and the overall mental component score (51.8 vs. 49.1, respectively) were comparable between both groups.

MW2012 Paediatric study (CIDS)

This study is a randomised (1:1), open-label, SOC-controlled, parallel group study in 145 hospitalised subjects (0-18 years of age) with deep partial or full thickness thermal burns affecting 1% to 30% of total body surface area (average TW area: 5.57% TBSA). Subjects were randomized to this medicinal product (2 g powder in 20 g gel per 180 cm^2 for 4 hours) or SOC (surgical and/or nonsurgical eschar removal procedures). There were three co-primary endpoints: the median time to complete eschar removal, the % of wound area surgically excised, and the cosmesis and function of the skin at 12 months after wound closure (Modified Vancouver Scar Scale score). Demographics and main results are presented in the table below.

A total of 145 patients were randomised and included in the full analysis set (FAS): 72 in the medicinal product arm and 73 in the SOC arm. Of these, 139 (95.9%) patients were treated and included in the safety analysis set (SAS): 69 (95.8%) in the medicinal product arm and 70 (95.9%) in the SOC treatment arm.

Age distribution was as follows (medicinal product vs. SOC): 0-11 months 4 vs. 4, 12-23 months 19 vs. 18, 24 months–3 years: 15 vs. 15, 4-11 y. 25 vs. 25 and 12-18 years: 9 vs. 11.
Overall, patients' age, ethnicity, height, weight and body mass index (BMI) were similar between treatment arms. On a patient level, the mean % TBSA of TWs was 5.85% for patients in the medicinal product arm vs. 5.30% in the SOC arm.

<u>Efficacy results:</u>

Compared to SOC, the medicinal product- treatment resulted in significantly shorter median time to complete eschar removal, significantly smaller mean percentage of the wound area surgically excised for eschar removal. Patients treated with this medicinal product had less surgical excisions compared to SOC. (see table)

Long term results (12 months)

With regard to cosmesis and function evaluated at 12 months, as measured by MVSS, non-inferiority of treatment with the medicinal product compared with SOC was demonstrated (p-value <0.0001), using a non-inferiority margin of 1.9.

Paediatric study MW2012 (CIDS)

	NexoBrid (N = 72)	SOC (N = 73)	p-value
Age (mean, SD)	5.71 (4.84)	5.83 (4.91)	
Outcomes			
Time to complete eschar removal			
Median, days (FAS)	0.99	5.99	0.0008
Percent wound area surgically excised (FAS)			
Mean ± SD (FAS)	1.5 ± 12.13	48.1 ± 46.58	< 0.0001
MVSS at 12 months			
Mean ± SD (FAS)	3.83 ± 2.876	4.86 ± 3.256	< 0.0001 (Non-inferiority shown)
Incidence of surgical excision (%)			
The proportion and number of patients who required surgical excision for eschar removal (FAS)*	8.33	64.38	
Mean time to last wound closure – observed data (days)			
Mean ± SD (FAS)	28.65 ± 16.56	27.74 ± 18.154	

*In a subgroup analysis by age group, superiority of this medicinal product over SOC was consistently demonstrated in each age group.

The mean change in haemoglobin following eschar removal procedures on both patient level and procedure level was lower for patients treated with the medicinal product compared to SOC.

Time to Reach Complete Wound Closure

The time to reach complete (>95%) wound closure on a TW level was comparable between this medicinal product and SOC treatment arms. In the pooled adult population, the Kaplan-Meier estimated median time to complete wound closure (clustered data of TWs in a patient), was (this medicinal product [N=280] vs. SOC [N=179]): 32 (95% CI: 29.0 - 34.0) days vs. 28 (95% CI: 24.0 - 29.0) days, respectively.
In the pooled paediatric population, the time to reach complete (>95%) wound closure on a TW level was comparable in the medicinal product and SOC treatment arms. The Kaplan-Meier estimated median time was (this medicinal product [N=89] vs. SOC [N=86]): 31 (95% CI: 27.0 - 36.0) days vs. 31 (95% CI: 24.0 - 37.0) days, respectively.
Results from both populations support the non-inferiority of the medicinal product compared with SOC based on a 7-day non-inferiority margin.

5.2 Pharmacokinetic properties

Adults population

Absorption

Exploratory pharmacokinetic analyses were performed in a subset of patients treated with this medicinal product who participated in study MW2010 (DETECT)

Evidence of systemic serum exposure was observed in all patients after topical administration of this medicinal product. In general, it appears to be rapidly absorbed, with a median T_{max} value of 4.0 hours (duration of treatment application). medicinal product exposure was observed with quantifiable serum concentrations through 48 hours post dose administration.

Exposure results from study MW2010are listed in the table below.
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.

There was a statistically significant correlation between serum C_{max} and AUC_{0-4} values versus dose or %TBSA, suggesting a dose / treatment area dependent increase in exposure. The depth of the treated wound has negligible impact on systemic exposure.

Summary of PK parameters* measured in all patients from Study MW2010

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)
MW2010	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 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 α_2-macroglobulin and α_1-antichymotrypsin.

Elimination

The mean elimination half-life values ranged between 12 and 17 hours, supporting the decreased presence in serum at 72 hours post treatment.
When evaluated, a majority of patients had no quantifiable concentrations after 72 hours.

Paediatric population

Exploratory pharmacokinetic analyses were performed in a PK sub-study of study MW2012 (CIDS). The analyses were performed on serum medicinal product concentration versus time data.

PK blood samples were collected from 16 patients treated with the medicinal product. All patients were treated with a single application.
Evidence of systemic serum exposure was observed in all 16 patients for which PK samples were available.
Concentrations increased relatively rapidly, with median Tmax values between 2 to 4 hours, corresponding to the period of topical administration.
Systemic exposure to the medicinal product was in correlation with the topical dose applied.
Exposure results are listed in the table below.

Summary of PK parameters measured in patients from study MW2012

(Age group years)	N*	T_{max} (h)	C_{max} (ng/mL)	Cmax/Dose (ng/mL/g)	AUC $_{0-4}$ (h*ng/mL)	AUC $_{0-4}$/ Dose (h*ng/mL/g)	AUClast (h*ng/mL)	AUClast/Dose (h*ng/mL/g)
<2[a]	2	2.00	200	66.7	476	159	876	292
4-11[b]	5	4.0 (2.0-4.0)	205±169	32.8±23.9	416±259	67.9±44.7	2240±2220	366±350
12-18[c]	3	4.0 (2.0-4.0)	180±114	19.2±7.50	499±315	53.3±20.4	1560±887	174±67.4

* Ten subjects were included in the main PK analyzes.

Elimination
A majority of the patients had no quantifiable concentrations of the medicinal product after 48 hours, with no quantifiable concentrations in any patient at 72 hours

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 the medicinal product 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 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 four injections but severe clinical signs of toxicity (e.g. haemorrhages in several organs) were observed following the remaining two injections. Such effects could still be seen after the recovery period of 2 weeks.

The medicinal product toxicological findings in juvenile minipigs were similar to that of adults. Topical application of the medicinal product (0.09 g/g) to young pigs (2 months of age) did not cause any local and systemic toxicological relevant findings when applied to burn wounds in a formulation and in a dosage regimen relevant for the human use of the product. Following repeated intravenous injections of doses 4, 8 and 12 mg/kg every third day in juvenile mini-pigs, related changes were noted after the fifth dose on Day 10 in all dose groups. The findings included convulsions and reddening of the skin, as well as findings such as activity decreased, breathing difficulty, and ataxia in some of the animals.
A trend of increasing QT and QTc intervals was seen on Day 10 post dose in the treated animals. These values were obtained following significant clinical observations, described above.

In embryo-foetal development studies in rats and rabbits, intravenously administered this 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 C_{max}). Since this medicinal product was poorly tolerated by the parent animals, these studies are not considered relevant for human risk assessment. This medicinal product 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

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.

<u>Gel preparation (mixing powder with gel)</u>

- 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 Germany GmbH
Hans-Sachs-Strasse 100
65428 Rüsselsheim
Germany

e-mail: info@mediwound.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/803/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18.12.2012
Date of latest renewal: 12.08.2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

MediWound Ltd.
42 Hayarkon St.
81227 Yavne
Israel

Name and address of the manufacturer responsible for batch release

Diapharm GmbH & Co. KG
Am Mittelhafen 56 48155 Münster
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic safety update reports (PSURs)
The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch in each Member State, the Marketing Authorisation Holder MAH shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals in specialist burn centres who are expected to use and/or prescribe this medicinal product receive a specific training and are provided with an Educational pack.

MAH should undertake a controlled distribution of this medicinal product to ensure that the product is not available for use at a centre until at least one surgeon at the centre has received formal training in the use of

this medicinal product. This is in addition to the educational material which all potential users should receive.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Healthcare Professional information pack

The Healthcare Professional information pack should be a step by step treatment guide that includes information on the following key elements:

Before prescribing this medicinal product

- The limitation of the total area that can be treated to 15% TBSA in adults and children/adolescents >3 years of age; limitation to 10 % TBSA in children 0 - 3 years of age.
- The risk of allergic reaction and of cross reactivity and the contraindication in patients allergic to pineapple and papain or to previous application of the product
- The risk of increased mortality in patients with cardiopulmonary diseases

Before applying this medicinal product

- The need for pain management
- The need for wound cleansing and preparation before treatment with
    - Application of a dressing soaked with an antibacterial solution for two hours before medicinal product application
    - Protection of surrounding skin areas
- The method of preparation of the medicinal product and of its application to wound area

After applying this medicinal product

- The removal of this medicinal product and of dissolved eschar
- The wound assessment and the warning against any repeat treatment
- The wound management after this medicinal product treatment with
    - Application of a dressing soaked with an antibacterial solution for two hours
    - Performance of grafting procedures as soon as possible after debridement
- The fact that this medicinal product may cause an allergic reaction, an increased tendency to bleed and severe local irritation and that patients should be monitored for signs or symptoms of these
- The fact that patients should be monitored for signs and symptoms of wound and systemic infections

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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).

3. LIST OF EXCIPIENTS

Excipients for the powder: Acetic acid, ammonium sulphate.
Excipients for the gel: Carbomer 980, disodium phosphate anhydrous, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and gel for gel

1 vial of 5 g powder
1 bottle of 50 g of gel

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Powder and gel to be mixed before application.

Read the package leaflet before use.

For single use only.

Cutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light. Store upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MediWound Germany GmbH
Hans-Sachs-Strasse 100
65428 Rüsselsheim
Germany
e-mail: info@mediwound.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/803/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

NexoBrid powder (vial)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

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).

3. LIST OF EXCIPIENTS

Excipients: Acetic acid, ammonium sulphate.

4. PHARMACEUTICAL FORM AND CONTENT

Powder for gel
5 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Powder and gel to be mixed before application.

Read the package leaflet before use.

For single use only.

Cutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated (2°C-8°C).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSEDMEDICINAL PRODUCTS OR WASTE MATERIALS DEREIvED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/803/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

Gel for NexoBrid powder

1. NAME OF THE MEDICINAL PRODUCT

Gel for NexoBrid 5 g

2. STATEMENT OF ACTIVE SUBSTANCE

Concentrate of proteolytic enzymes enriched in bromelain: 0.09 g/g (or 5 g/55 g gel) after mixing.

3. LIST OF EXCIPIENTS

Excipients: Carbomer 980, disodium phosphate anhydrous, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Gel
50 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Powder and gel to be mixed before application.

Read the package leaflet before use.

For single use only.

Cutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated (2°C-8°C).
Do not freeze.

Store in the original package in order to protect from light. Store upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you or your child get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NexoBrid is and what it is used for

What NexoBrid is
NexoBrid contains a mixture of enzymes called "concentrate of proteolytic enzymes enriched in bromelain", which is produced from an extract from the stem of the pineapple plant.

What NexoBrid is used for
NexoBrid is used in adults, adolescents and children of all ages to remove burnt tissue from deep or partially deep burn wounds of the skin.
Using NexoBrid may reduce the need for, or the extent of, surgical removal of burnt tissue and/or skin transplantation.

2. What you need to know before NexoBrid is used

NexoBrid must not be used:
- if you or your child are allergic to bromelain
- if you or your child are allergic to pineapples
- if you or your child are allergic to papaya/papain
- if you or your child are allergic to any of the other ingredients of the powder or gel (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before NexoBrid is used if:

- you or your child have a heart disease;
- you or your child have diabetes;
- you or your child have an active peptic ulcer in the stomach,
- you or your child have a vascular disease (with vascular occlusion);
- you or your child have enlarged veins in the area close to the burn;

- you or your child have implants or a pacemaker or a vascular shunt;
- you or your child have problems with bleeding or if you or your child take blood-thinners;
- your or your child's wound(s) came into contact with chemicals or other hazardous substances;
- you or your child have a lung disease;

- your or your child's lung has been, or may have been damaged by inhalation of smoke;
- you or your child are allergic to latex, bee stings, or olive tree pollen. If so, you or your child may also experience allergic reactions to NexoBrid.

Allergic reactions can cause, for example, breathing difficulties, swelling of the skin, hives, other skin reactions, redness of the skin, low blood pressure, fast heart rate and abdominal discomfort, or a combination of such effects. If you or your child notice any of these signs or symptoms, inform your doctor or caregiver immediately.
Allergic reactions can be severe and require medical treatment.
In case of skin contact, rinse NexoBrid off with water. This is to make an allergic reaction to NexoBrid less likely.

The use of NexoBrid to remove burnt tissue may lead to fever, to wound inflammation or wound infection, and possibly to general infection. You or your child may be checked regularly for these conditions and may receive medicines to prevent or treat infections.

NexoBrid may reduce the ability of blood to form clots, which increases the risk of bleeding. NexoBrid should be used with caution if you or your child are treated with medicines that reduce your blood's ability to form clots (so-called blood-thinners) or if you or your child have a general tendency to bleed, a stomach ulcer, blood poisoning, or another condition that could cause you or your child to bleed. After treatment with NexoBrid your doctor may check blood coagulation levels.

Direct contact of NexoBrid with the eyes should be avoided. If NexoBrid goes into the eyes, wash them with lots of water for at least 15 minutes.

To prevent wound-healing problems, the treated burn wound will be covered as soon as possible by temporary or permanent skin substitutes or dressings.

NexoBrid should not be used in chemical burn wounds, electrical burns, foot burns in diabetic patients and patients with occlusive vascular disease, in contaminated wounds and wounds where NexoBrid could come in contact with foreign materials (for example, implants, pacemakers, and shunts) or large blood vessels, the eyes or other important body parts.
NexoBrid should be used with caution in areas of varicose veins (enlarged twisted veins), to prevent risk of bleeding from them.

Other medicines and NexoBrid
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Your doctor will be cautious and watch for signs of reduced blood coagulation or bleeding when prescribing other medicines that affect blood coagulation, because NexoBrid may reduce blood coagulation.

Other medicines and NexoBrid
Tell your doctor if you or your child are taking, have recently taken or might take any other medicines.

Your doctor will be cautious and watch for signs of reduced blood coagulation or bleeding when prescribing other medicines that affect blood coagulation, because NexoBrid may reduce blood coagulation.

NexoBrid may:
- increase the effects of certain medicines that are inactivated by a liver enzyme called CYP2C8 and CYP2C9. This is because NexoBrid can be absorbed from the burn wound into the blood stream. Examples of such medicines are:
  - amiodarone (used to treat certain forms of irregular heartbeat),
  - amodiaquine and chloroquine (used to treat malaria and some forms of inflammation),
  - fluvastatin (used to treat high cholesterol),
  - pioglitazone, repaglinide, tolbutamide and glipizide (used to treat diabetes),

- paclitaxel(used to treat cancer),
- torasemide (used to increase urine flow),
- ibuprofen (used to treat fever, pain and some forms of inflammation),
- losartan (used to treat high blood pressure),
- celecoxib (used to treat some forms of inflammation),
- warfarin (used to reduce blood coagulation), and
- phenytoin (used to treat epilepsy).

- intensify your or your child's reaction to the cancer medicines fluorouracil and vincristine.
- cause an unwanted drop in blood pressure when you or your child are treated with medicines called ACE inhibitors, which are used to treat high blood pressure and other conditions.
- increase drowsiness when used at the same time with medicines that can cause drowsiness. These medicines include, for example, sleep medications, so-called tranquilizers, some pain medications and antidepressants.Silver sulfadiazine or povidone-iodine at the wound site may decrease the efficacy of the medicinal product.

If you are not sure whether you or your child are taking any of the medicines mentioned above, ask your doctor before NexoBrid is used.

Pregnancy and breast-feeding
The use of NexoBrid during pregnancy is not recommended.
As a precautionary measure, you should not breast-feed for at least 4 days after NexoBrid application.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, talk to your doctor or pharmacist before this medicine is used.

3. How NexoBrid is used

NexoBrid is for use by specialists in burn clinics only. It will be prepared directly before use and applied by a doctor or another healthcare professional.

5 g NexoBrid powder mixed in 50 g gel is applied 1.5 to 3 millimetres thick to a burn wound area of 2.5 percent of an adult patient's body surface.

It should be left for 4 hours, and then be removed. A second and subsequent application is not recommended.

- NexoBrid should not be applied to more than 15% of the total body surface in adults and children/adolescents from 4 – 18 years.
- In children aged 0-3 years this medicine should not be applied to more than 10% of the total body surface.

Instructions for the preparation of the NexoBrid gel are given at the end of this leaflet in the section intended for medical or healthcare professionals.

Before it is applied to a burn wound, NexoBrid powder is mixed into a gel. It should be used within 15 minutes after mixing.

- NexoBrid will be applied to a wound area that is clean, blister free, and moist.

- Other medicines (such as silver sulfadiazine or povidone-iodine) will be removed from the wound area before NexoBrid is applied.

- Before NexoBrid application, a dressing soaked with an antibacterial solution will be applied for 2 hours.

- You or your child will be given appropriate medicine to prevent and treat pain at least 15 minutes before NexoBrid is applied and before removal.

- After NexoBrid and the dead tissue have been removed from the wound, a dressing soaked with an antibacterial solution will be applied for an additional 2 hours.

- The vial containing the powder, gel bottle, and the prepared gel are for single use only.

If too much NexoBrid is used
If too much NexoBrid gel is applied on a burn wound, excess gel may be wiped off.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions to NexoBrid can occur and can cause, for example, breathing difficulties, swelling of the skin, hives, redness of the skin, low blood pressure, fast heart rate and sickness/vomiting/stomach cramp, or a combination of such effects. If you or your child notice any of these symptoms or signs, inform your doctor or caregiver immediately.

Very common (may affect more than 1 in 10 people)
- Fever

Common (may affect up to 1 in 10 people)
- Pain in the treated area of the burn wound (even if medicines are used to prevent or lessen pain caused by the removal of burnt tissue)
- Infection of the burn wound, including infection of the skin around the wound (cellulitis)
- Complications of the wound including wound deepening, wound opening, wounds drying out and breaking down, failure of skin grafts to heal properly.
- Rash or redness in the area around the burn wound
- Non serious allergic reactions such as rash.
- Rapid heartbeat
- Itching in the burn wound area. Itching of the burn wound area, is very frequent as part of the normal burn healing process.

Uncommon
- Bruising in the wound area

Not known (frequency cannot be estimated from the available data)
- Serious allergic reactions including anaphylaxis

Reporting of side effects
If you or your child get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How NexoBrid is stored

Keep this medicine out of the sight and reach of children.

Do not use NexoBrid after the expiry date which is stated on the label of the vial, bottle, and box after "EXP". The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C-8°C).

NexoBrid must be stored upright to keep the gel at the bottom of the bottle and in the original package to protect from light.
Do not freeze.

NexoBrid should be used within 15 minutes after mixing the powder with the gel.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nexobrid contains

- The active substance (in the powder in the vial) is a concentrate of proteolytic enzymes enriched in bromelain: one vial contains5 g, corresponding to 0.09 g/g concentrate of proteolytic enzymes enriched in bromelain after mixing.
- The other ingredients are:
  - for the powder: ammonium sulphate and acetic acid
  - and for the gel: carbomer 980, disodium phosphate anhydrous, sodium hydroxide, and water for injections.

What NexoBrid looks like and contents of the pack
NexoBrid is provided as a powder and gel for gel (powder in a vial (5 g) and gel in a bottle (50 g)), pack size of 1 (a pack contains one vial of powder and one bottle of gel)

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

For any information about this medicine, please contact the Marketing Authorisation holder.

Marketing Authorisation Holder

MediWound Germany GmbH
Hans-Sachs-Strasse 100
65428 Rüsselsheim
Germany
e-mail: info@mediwound.com

Manufacturer
Diapharm GmbH & Co. KG
Am Mittelhafen 56 48155 Münster
Germany

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Preparation and administration

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).

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.

Preparation of patient and wound area

- A total wound area of not more than 15% TBSA can be treated by NexoBrid in adults and children/adolescents >3 years of age; in children 0 - 3 years of age not more than 10% TBSA can be treated.
- 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 NexoBrid and prevent eschar removal by NexoBrid.
- Dressing soaked with an antibacterial solution must be applied for 2 hours.
- All topically applied antibacterial medicinal products must be removed before applying NexoBrid. 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 in order 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). The medicinal product should be used with caution in areas of varicose veins, to prevent erosion of the veins' wall, and the risk of bleeding.
- 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 gel preparation (mixing powder with gel)

- The NexoBrid powder and gel are sterile. Aseptic technique must be used when mixing NexoBrid powder with the gel. The powder should not be inhaled. Wearing of gloves and protective clothing as well as eye shielding glasses and surgical mask, is required.
- The NexoBrid 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.
- NexoBrid powder is then transferred into the corresponding gel bottle.
- NexoBrid powder and gel must be mixed thoroughly until a uniform, slightly tan to slightly brown mixture is obtained. This usually requires mixing the NexoBrid powder and the gel for 1 to 2 minutes.
- NexoBrid gel should be prepared at the patient’s bedside.

NexoBrid application

- 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, NexoBrid must be applied topically to the 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 should 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 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
- Removal of NexoBrid 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 NexoBrid application.
- 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 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 should be applied.
- Before application of the grafts and 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.

<u>Recommendations for safe handling</u>

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

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 NexoBrid powder with the gel, appropriate handling, including wearing of gloves and protective clothing as well as eye shielding glasses and surgical mask, is required. The powder should not be inhaled.

Avoid accidental eye exposure. In case of eye exposure, irrigate exposed eyes with copious amounts of water for at least 15 minutes. In case of skin exposure, rinse NexoBrid off with water.

<u>Disposal</u>

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