

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

NexoBrid 2 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).

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

NexoBrid should only be applied by trained healthcare professionals in specialist burn centres.

Posology

2 g NexoBrid powder in 20 g gel is applied to a burn wound area of 100 cm².

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

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

Special populations

Renal impairment

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

Hepatic impairment

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

Elderly patients

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

Paediatric population

The safety and efficacy of NexoBrid in children and adolescents younger than 18 years have not yet been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made.

NexoBrid 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.

NexoBrid should be applied to a clean, keratin-free (blisters removed), and moist wound area.

Topically applied medicinal products (such as silver sulfadiazine or povidone-iodine) at the wound site must be removed and the wound must be cleansed prior to NexoBrid application.

See section 6.6 for instructions on NexoBrid gel preparation.

Preparation of patient and wound area

A total wound area of not more than 15% TBSA can be treated with NexoBrid (see also section 4.4, Coagulopathy).

- 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 interfere with the activity of NexoBrid by decreasing its efficacy.
- The area from which you wish to remove the eschar must be surrounded with a sterile paraffin ointment adhesive barrier by applying it a few centimetres outside of the treatment area (using a dispenser). The paraffin layer must not come into contact with the area to be treated to avoid covering the eschar, thus isolating the eschar from direct contact with NexoBrid. To prevent possible irritation of abraded skin by inadvertent contact with NexoBrid, such areas can be protected by a layer of a sterile fatty ointment.
- Sterile isotonic sodium chloride 9 mg/ml (0.9%) solution must be sprinkled on the burn wound. The wound must be kept moist during the application procedure.

NexoBrid application

- Within 15 minutes of mixing, NexoBrid must be applied topically to the moistened burn wound, at a thickness of 1.5 to 3 millimetres.
- The wound must then be covered with a sterile occlusive film dressing that adheres to the sterile adhesive barrier material applied as per the instruction above (see *Preparation of patient and wound area*). The NexoBrid gel must fill the entire occlusive dressing, and special care should be taken not to leave air under this occlusive dressing. Gentle pressing of the occlusive

dressing at the area of contact with the adhesive barrier will ensure adherence between the occlusive film and the sterile adhesive barrier and achieve complete containment of NexoBrid on the treatment area.

- The dressed wound must be covered with a loose, thick fluffy dressing, held in place with a bandage.
- The dressing must remain in place for 4 hours.

Removal of NexoBrid

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

Wound care after debridement

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

See section 4.4.

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

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

Concentrate of proteolytic enzymes enriched in bromelain is systemically absorbed from burn wound areas (see section 5.2).

NexoBrid is not recommended for use on:

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

Use in patients with cardiopulmonary and pulmonary disease

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

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

Burns for which there is limited or no experience

There is no experience of the use of NexoBrid on:

- perineal and genital burns.
- electrical burns.

There is limited information on the use of NexoBrid on facial burn wounds.

NexoBrid must be used with caution in such patients. Eyes should be carefully protected during treatment of facial burns using adhesive barrier petroleum ointment.

There is limited pharmacokinetic data in patients with TBSA of more than 15%. Due to safety considerations (see also section 4.4, Coagulopathy) NexoBrid should not be applied to more than 15% Total Body Surface Area (TBSA).

Prevention of wound complications

In NexoBrid studies wounds with visible dermal remnants were allowed to heal by spontaneous epithelialisation. In several cases adequate healing did not occur and autografting was required at a later date, leading to significant delays in wound closure which is associated with increased risk of wound-related complications. Therefore, wounds with areas of full-thickness and deep burn should be autografted as soon as possible after NexoBrid debridement (see section 5.1 for study results). Careful consideration should also be given to placing permanent skin covers (e.g. autografts) on deep partial thickness wounds soon after NexoBrid debridement. See also section 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.

Eye protection

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

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

Hypersensitivity reactions, skin exposure

There have been reports of serious allergic reactions including anaphylaxis (with manifestations such as rash, erythema, hypotension, tachycardia) in patients undergoing debridement with NexoBrid.

Allergic reactions to bromelain have been reported in the literature (including anaphylactic reactions and other immediate-type reactions with manifestations such as bronchospasm, angioedema, urticaria, and mucosal and gastrointestinal reactions). 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.

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

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

Coagulopathy

It is not known if NexoBrid application has any clinically relevant effect on haemostasis. An increase in heart rate (including tachycardia), reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported in the literature as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. During the clinical development of NexoBrid, there was no indication of an increased bleeding tendency or bleeding at the site of debridement.

NexoBrid should be used with caution in patients with disorders of coagulation, low platelet counts and increased risk of bleeding from other causes e.g. peptic ulcers and sepsis. Patients should be monitored for possible signs of coagulation abnormalities.

Monitoring

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

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

Removal of topically applied antibacterial medicinal products before NexoBrid application

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with NexoBrid have been performed.

Reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. Caution and monitoring is therefore needed when prescribing concomitant medicinal products that affect coagulation. See also section 4.4.

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

repaglinide, rosiglitazone, sorafenib and torasemide) and CYP2C9 substrates (including ibuprofen, tolbutamide, glipizide, losartan, celecoxib, warfarin, and phenytoin).

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

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

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

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 NexoBrid in pregnant women. Animal studies are insufficient to properly assess the potential of NexoBrid to interfere with embryonal/foetal development (see section 5.3).

Since the safe use of NexoBrid during pregnancy has not yet been established, NexoBrid 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 newborns/infants cannot be excluded. Breast-feeding should be discontinued at least 4 days from NexoBrid application initiation.

Fertility

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

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 of the use of NexoBrid are local pain and transient pyrexia/hyperthermia. When NexoBrid was used in a regimen which included recommended preventive analgesia as routinely practiced for extensive dressing changes in burn patients as well as antibacterial soaking of the treatment area before and after NexoBrid application (see section 4.2), pain was reported in 3.6% of patients, pyrexia/hyperthermia in 19.1% of patients. The frequency of pain and pyrexia/hyperthermia was higher without these precautionary measures (see below).

Tabulated list of adverse reactions

The following definitions apply to the frequency terminology used hereafter:

Very common ($\geq 1/10$)
Common ($\geq 1/100$ to $< 1/10$)
Uncommon ($\geq 1/1,000$ to $< 1/100$)
Rare ($\geq 1/10,000$ to $< 1/1,000$)
Very rare ($< 1/10,000$)
Not known (cannot be estimated from the available data).

The frequencies of the adverse reactions presented below reflect the use of NexoBrid to remove eschar from deep partial- or full-thickness burns in a regimen with local antibacterial prophylaxis, recommended analgesia, as well as coverage of the wound area after application of NexoBrid for 4 hours with an occlusive dressing for containment of NexoBrid on the wound.

An asterisk (*) indicates that additional information on the respective adverse reaction is provided below the list of adverse reactions.

Infections and infestations

Common: Wound infection

Skin and subcutaneous tissue disorders/

Common: Wound complication*

General disorders and administration site conditions

Very common: Pyrexia/hyperthermia*

Common: Local pain*

Immune system disorders

Not known: Serious allergic reactions including anaphylaxis

Description of selected adverse reactions

Pyrexia/hyperthermia

In studies implementing routine antibacterial soaking of the treatment area before and after NexoBrid application (see section 4.2) pyrexia or hyperthermia was reported in 19.1% of patients treated with NexoBrid and in 15.8% of the control patients treated according standard of care. In the NexoBrid group, the event was graded as mild, moderate or severe in 9.1%, 9.1%, and 0% of patients, respectively.

In studies without antibacterial soaking, pyrexia or hyperthermia was reported in 35.6% of NexoBrid-treated patients compared with 18.6% in control patients. In the NexoBrid group, the event was graded as mild, moderate or severe in 30.0%, 5.6% and 1.1% of patients, respectively.

Pain

In studies where the NexoBrid regimen included recommended preventive analgesia as routinely practiced for extensive dressing changes in burn patients (see section 4.2) local pain was reported in 3.6% of patients treated with NexoBrid and in 4.0% of the control patients treated according to standard of care. In the NexoBrid group, the event was graded as mild, moderate or severe in 0.9%, 0.9%, and 1.8% of patients, respectively.

In studies where analgesia was provided in NexoBrid-treated patients on an on-demand basis, local pain was reported in 23.3% of patients treated with NexoBrid and in 11.4% of the control patients. In the NexoBrid group, the event was graded as mild, moderate or severe in 6.7%, 7.8% and 8.9% of patients, respectively.

Wound complications

In phase 2 and phase 3 clinical studies, certain types of wound complications were reported more frequently in the NexoBrid group than in the group treated according to the study sites' Standard of

Care (SOC). These events included: wound deepening or desiccation (decomposition) in 5 patients (2.4%) with NexoBrid and 0 with SOC as well as (partial) graft failure in 6 patients (2.9%) with NexoBrid and 2 (1.6%) with SOC (see section 4.4).

General infections

In phase 2 and phase 3 clinical studies general infections (not wound related. e.g. urinary tract infections, viral infections) were reported more frequently in the NexoBrid group (0.147 events per patient) than in the group treated according to SOC (0.079 events per patient).

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.

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.

Concentrate of proteolytic enzymes enriched in bromelain is a debriding agent, applied topically for removal of eschar in deep partial- and full-thickness burns.

Mechanism of action

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

Clinical efficacy

During clinical development, a total of 362 patients were treated with the concentrate of proteolytic enzymes enriched in bromelain.

The efficacy of NexoBrid in humans was evaluated, compared to standard of care, in a randomised, multi-centre, multi-national, open-label, confirmatory phase 3 study in hospitalised patients with deep partial- and/or full-thickness thermal burns of 5 to 30% Total Body Surface Area (TBSA), but with total burn wounds of no more than 30% TBSA.

NexoBrid (2 g/100 cm², corresponding to 0.02 g/cm²) was used as described in section 4.2.

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

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

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

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

The co-primary endpoints for the efficacy analysis were:

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

This 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.

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The following table shows results in mixed wounds. The comparisons in mixed wounds should be interpreted with caution since they are based on groups that are not fully randomized and the mixed wounds treated by NexoBrid were overall larger and had a larger full thickness area.

Mixed wounds (with partial and full-thickness area) requiring excision/dermabrasion (surgery)

	NexoBrid (Number of wounds)	SOC (Number of wounds)
% of wounds requiring surgery	41.7% (20/48)	78.3% (47/60)
% of wound area excised or dermabraded	25.5% (n=48)	64.0% (n=60)

Mixed wounds (with partial and full-thickness area) autografted

	NexoBrid (Number of wounds)	SOC (Number of wounds)
All mixed burns baseline characteristics	48 wounds	60 wounds
Size: % mean TBSA	7.43	6.33
Depth:		
Superficial (%TBSA)	0.67	0.92
DPT (% TBSA)	3.85	3.13
FT (% TBSA)	2.90	2.29
Incidence of autograft	70.8% (34/48)	63.3% (38/60)
% wound area autografted	55.5% (n=48)	45.8% (n=60)

The following table shows the time to complete wound closure from start of debridement.*

Wound Type	NexoBrid	SOC
	Days (mean ± SD) (Number of wounds)	Days (mean ± SD) (Number of wounds)
All wounds (ITT ¹)	30.5 ± 16.9 (154)	26.1 ± 16.0 (164)
Non-autografted wounds (ITT)	23.9 ± 13.0 (95)	24.5 ± 14.1 (85)
Autografted wounds (ITT)	41.0 ± 17.3 (59)	27.8 ± 17.7 (79)
Deep Partial Thickness wounds	26.6 ± 15.4 (101)	23.7 ± 13.6 (87)
Full Thickness wounds	31.9 ± 10.1 (7)	36.3 ± 26.0 (14)
Mixed wounds (deep partial and full thickness)	40.2 ± 17.1 (44)	27.7 ± 15.8 (59)
Non-autografted mixed wounds	29.5 ± 12.1 (11)	30.3 ± 15.5 (22)

Autografted mixed wounds	43.7 ± 17.3 (33)	26.2 ± 16.0 (37)
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*These comparisons should be interpreted with caution since they are based on groups that are not fully randomized.

¹ ITT (Intent To Treat population): all randomized patients

The difference in time to complete wound closure is mainly related to the wound care strategy applied by the physician, where an attempt to minimise grafting and allow for spontaneous epithelialisation of the wound areas that still have dermis may prolong time to first autograft (time to autograft: NexoBrid: 14.7 days vs. SOC: 5.9 days) and hence prolong complete wound closure.

Paediatric population

Efficacy data generated in this study from a subgroup analysis for children and adolescents are summarised below. The available data are limited and NexoBrid 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.

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The European Medicines Agency has deferred the obligation to submit the results of studies with NexoBrid 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).

5.2 Pharmacokinetic properties

Absorption

The extent of systemic absorption from a burn wound, C_{max} , T_{max} , AUC, and $t_{1/2}$ of bromelain from NexoBrid have been investigated in 16 burn patients with partial-thickness (mid- and deep-dermal) thermal burns. Average TBSA was 10%. 60% of the treated wounds area was partial thickness and/or full thickness. NexoBrid was applied once to the burn wound at a dose of 2 g NexoBrid Powder/20 g gel/100 cm² of skin.

NexoBrid serum concentrations were determined using a modified sandwich electrochemiluminescence (ECL) immunoassay.

The range of total dose applied was 5 to 30 g concentrate of proteolytic enzymes enriched in bromelain from NexoBrid. In 4 patients, having received a dose of 5, 9, 12 and 17 g, respectively, there were indications of markedly higher systemic absorption.

C_{max} was 6020 ± 5020 ng/ml (mean \pm SD) for the group of 15 patients, with a range of 888 to 15,700 ng/ml. In the 4 patients with indications of higher absorption, dose-normalised C_{max} ranged from 788-900 ng/ml per gram of NexoBrid. In the other patients, dose-normalised C_{max} ranged from 141-523 ng/ml per gram of NexoBrid.

A C_{max} of 40 μ g/ml may be possible in humans administered NexoBrid under licensed conditions, when it is considered that PK has only been evaluated in patients with largely superficial burns, receiving half the maximum dose.

The AUC from time zero to 48 hours after administration (AUC_{last}) was $43,400 \pm 46,100$ ngh/ml (mean \pm SD) for the group of 15 patients, with a range of 4560-167,000 ngh/ml. In the patients with indications of higher absorption, dose-normalised (per gram of NexoBrid) AUC_{last} ranged from 4500-9820 ngh/ml per gram of NexoBrid. In the other patients, dose-normalised AUC_{last} ranged from 887-3930 ngh/ml per gram of NexoBrid.

These results for C_{max} and AUC_{last} indicate that systemic absorption may depend both on the applied NexoBrid dose (proportional to the covered wound area) and other, patient-specific factors.

T_{max} for 10 of the 15 patients was 2 hours and in 5 patients T_{max} was 4 hours.

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:

Terminal half-life (determined using data from 16 to 48 hours post-dose for 12 patients) was 11.7 ± 3.5 hours (mean \pm SD), with a range from 8.5 to 19.9 hours.

Paediatric population

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

5.3 Preclinical safety data

NexoBrid was well tolerated 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 dosage to 15% TBSA*) but higher doses were overtly toxic, causing haemorrhage in several tissues. Repeated intravenous injections of doses up to 12 mg/kg every third day in the mini-pig were well tolerated for the first three injections but severe clinical

signs of toxicity (e.g. haemorrhages in several organs) were observed following the remaining three injections. Such effects could still be seen after the recovery period of 2 weeks.

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

NexoBrid powder

Ammonium sulphate

Acetic acid

Gel

Carbomer 980

disodium phosphate anhydrous

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Topically applied medicinal products (such as silver sulfadiazine or povidone-iodine) at the wound site must be removed and the wound cleansed prior to NexoBrid application. Remaining antibacterial medicinal products may interfere with the activity of NexoBrid by decreasing its efficacy.

This medicinal product must not be mixed with other medicinal products.

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).

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, angioedema, urticaria, and mucosal and gastrointestinal reactions. This should be considered when mixing NexoBrid powder with the gel. The powder should not be inhaled.. See also section 4.4.

Accidental eye exposure must be avoided. In case of eye exposure, exposed eyes must be irrigated with copious amounts of water for at least 15 minutes. In case of skin exposure, NexoBrid must be rinsed off with water.

NexoBrid gel preparation (mixing powder with gel)

- The NexoBrid powder and gel are sterile. An aseptic technique must be used when mixing the powder with the gel.
- The vial with NexoBrid powder must be shaken vigorously to fragment the NexoBrid powder cake.
- 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. If necessary, a sterile spatula can be used to break the dry powder cake in its vial prior to transfer.
- 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
Eisenstrasse 5
65428 Rüsselsheim
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/803/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18.12.2012

Date of latest renewal:

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>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

NexoBrid 5 g powder and gel for gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

NexoBrid should only be applied by trained healthcare professionals in specialist burn centres.

Posology

5 g NexoBrid powder in 50 g gel is applied to a burn wound area of 250 cm².

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

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

Special populations

Renal impairment

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

Hepatic impairment

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

Elderly patients

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

Paediatric population

The safety and efficacy of NexoBrid in children and adolescents younger than 18 years have not yet been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made.

NexoBrid 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.

NexoBrid should be applied to a clean, keratin-free (blisters removed), and moist wound area.

Topically applied medicinal products (such as silver sulfadiazine or povidone-iodine) at the wound site must be removed and the wound must be cleansed prior to NexoBrid application.

See section 6.6 for instructions on NexoBrid gel preparation.

Preparation of patient and wound area

A total wound area of not more than 15% TBSA can be treated with NexoBrid (see also section 4.4, Coagulopathy).

- 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 interfere with the activity of NexoBrid by decreasing its efficacy.
- The area from which you wish to remove the eschar must be surrounded with a sterile paraffin ointment adhesive barrier by applying it a few centimetres outside of the treatment area (using a dispenser). The paraffin layer must not come into contact with the area to be treated to avoid covering the eschar, thus isolating the eschar from direct contact with NexoBrid. To prevent possible irritation of abraded skin by inadvertent contact with NexoBrid, such areas can be protected by a layer of a sterile fatty ointment.
- Sterile isotonic sodium chloride 9 mg/ml (0.9%) solution must be sprinkled on the burn wound. The wound must be kept moist during the application procedure.

NexoBrid application

- Within 15 minutes of mixing, NexoBrid must be applied topically to the moistened burn wound, at a thickness of 1.5 to 3 millimetres.
- The wound must then be covered with a sterile occlusive film dressing that adheres to the sterile adhesive barrier material applied as per the instruction above (see *Preparation of patient and wound area*). The NexoBrid gel must fill the entire occlusive dressing, and special care should be taken not to leave air under this occlusive dressing. Gentle pressing of the occlusive

dressing at the area of contact with the adhesive barrier will ensure adherence between the occlusive film and the sterile adhesive barrier and achieve complete containment of NexoBrid on the treatment area.

- The dressed wound must be covered with a loose, thick fluffy dressing, held in place with a bandage.
- The dressing must remain in place for 4 hours.

Removal of NexoBrid

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

Wound care after debridement

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

See section 4.4.

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

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

Concentrate of proteolytic enzymes enriched in bromelain is systemically absorbed from burn wound areas (see section 5.2).

NexoBrid is not recommended for use on:

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

Use in patients with cardiopulmonary and pulmonary disease

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

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

Burns for which there is limited or no experience

There is no experience of the use of NexoBrid on:

- perineal and genital burns.
- electrical burns.

There is limited information on the use of NexoBrid on facial burn wounds.

NexoBrid must be used with caution in such patients. Eyes should be carefully protected during treatment of facial burns using adhesive barrier petroleum ointment.

There is limited pharmacokinetic data in patients with TBSA of more than 15%. Due to safety considerations (see also section 4.4, Coagulopathy) NexoBrid should not be applied to more than 15% Total Body Surface Area (TBSA).

Prevention of wound complications

In NexoBrid studies wounds with visible dermal remnants were allowed to heal by spontaneous epithelialisation. In several cases adequate healing did not occur and autografting was required at a later date, leading to significant delays in wound closure which is associated with increased risk of wound-related complications. Therefore, wounds with areas of full-thickness and deep burn should be autografted as soon as possible after NexoBrid debridement (see section 5.1 for study results). Careful consideration should also be given to placing permanent skin covers (e.g. autografts) on deep partial thickness wounds soon after NexoBrid debridement. See also section 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.

Eye protection

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

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

Hypersensitivity reactions, skin exposure

There have been reports of serious allergic reactions including anaphylaxis (with manifestations such as rash, erythema, hypotension, tachycardia) in patients undergoing debridement with NexoBrid.

Allergic reactions to bromelain have been reported in the literature (including anaphylactic reactions and other immediate-type reactions with manifestations such as bronchospasm, angioedema, urticaria, and mucosal and gastrointestinal reactions). 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..

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

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

Coagulopathy

It is not known if NexoBrid application has any clinically relevant effect on haemostasis. An increase in heart rate (including tachycardia), reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported in the literature as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. During the clinical development of NexoBrid, there was no indication of an increased bleeding tendency or bleeding at the site of debridement.

NexoBrid should be used with caution in patients with disorders of coagulation, low platelet counts and increased risk of bleeding from other causes e.g. peptic ulcers and sepsis. Patients should be monitored for possible signs of coagulation abnormalities.

Monitoring

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

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

Removal of topically applied antibacterial medicinal products before NexoBrid application

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with NexoBrid have been performed.

Reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. Caution and monitoring is therefore needed when prescribing concomitant medicinal products that affect coagulation. See also section 4.4.

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

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

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

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. 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 NexoBrid in pregnant women. Animal studies are insufficient to properly assess the potential of NexoBrid to interfere with embryonal/foetal development (see section 5.3).

Since the safe use of NexoBrid during pregnancy has not yet been established, NexoBrid 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 newborns/infants cannot be excluded. Breast-feeding should be discontinued at least 4 days from NexoBrid application initiation.

Fertility

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

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 of the use of NexoBrid are local pain and transient pyrexia/hyperthermia. When NexoBrid was used in a regimen which included recommended preventive analgesia as routinely practiced for extensive dressing changes in burn patients as well as antibacterial soaking of the treatment area before and after NexoBrid application (see section 4.2), pain was reported in 3.6% of patients, pyrexia/hyperthermia in 19.1% of patients. The frequency of pain and pyrexia/hyperthermia was higher without these precautionary measures (see below).

Tabulated list of adverse reactions

The following definitions apply to the frequency terminology used hereafter:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

The frequencies of the adverse reactions presented below reflect the use of NexoBrid to remove eschar from deep partial- or full-thickness burns in a regimen with local antibacterial prophylaxis, recommended analgesia, as well as coverage of the wound area after application of NexoBrid for 4 hours with an occlusive dressing for containment of NexoBrid on the wound.

An asterisk (*) indicates that additional information on the respective adverse reaction is provided below the list of adverse reactions.

Infections and infestations

Common: Wound infection

Skin and subcutaneous tissue disorders

Common: Wound complication*

General disorders and administration site conditions

Very common: Pyrexia/hyperthermia*

Common: Local pain*

Immune system disorders

Not known: Serious allergic reactions including anaphylaxis

Description of selected adverse reactions

Pyrexia/hyperthermia

In studies implementing routine antibacterial soaking of the treatment area before and after NexoBrid application (see section 4.2) pyrexia or hyperthermia was reported in 19.1% of patients treated with NexoBrid and in 15.8% of the control patients treated according standard of care. In the NexoBrid group, the event was graded as mild, moderate or severe in 9.1%, 9.1%, and 0% of patients, respectively.

In studies without antibacterial soaking, pyrexia or hyperthermia was reported in 35.6% of NexoBrid-treated patients compared with 18.6% in control patients. In the NexoBrid group, the event was graded as mild, moderate or severe in 30.0%, 5.6% and 1.1% of patients, respectively.

Pain

In studies where the NexoBrid regimen included recommended preventive analgesia as routinely practiced for extensive dressing changes in burn patients (see section 4.2) local pain was reported in 3.6% of patients treated with NexoBrid and in 4.0% of the control patients treated according to standard of care. In the NexoBrid group, the event was graded as mild, moderate or severe in 0.9%, 0.9%, and 1.8% of patients, respectively.

In studies where analgesia was provided in NexoBrid-treated patients on an on-demand basis, local pain was reported in 23.3% of patients treated with NexoBrid and in 11.4% of the control patients. In the NexoBrid group, the event was graded as mild, moderate or severe in 6.7%, 7.8% and 8.9% of patients, respectively.

Wound complications

In phase 2 and phase 3 clinical studies, certain types of wound complications were reported more frequently in the NexoBrid group than in the group treated according to the study sites' Standard of Care (SOC). These events included: Wound deepening or desiccation (decomposition) in 5 patients (2.4%) with NexoBrid and 0 with SOC as well as (partial) graft failure in 6 patients (2.9%) with NexoBrid and 2 (1.6%) with SOC (see section 4.4).

General Infections

In phase 2 and phase 3 clinical studies general infections (not wound related. e.g. urinary tract infections, viral infections) were reported more frequently in the NexoBrid group (0.147 events per patient) than in the group treated according to SOC (0.079 events per patient).

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.

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

Concentrate of proteolytic enzymes enriched in bromelain is a debriding agent, applied topically for removal of eschar in deep partial- and full-thickness burns.

Mechanism of action

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

Clinical efficacy

During clinical development, a total of 362 patients were treated with the concentrate of proteolytic enzymes enriched in bromelain.

The efficacy of NexoBrid in humans was evaluated, compared to standard of care, in a randomised, multi-centre, multi-national, open-label, confirmatory phase 3 study in hospitalised patients with deep partial- and/or full-thickness thermal burns of 5 to 30% Total Body Surface Area (TBSA), but with total burn wounds of no more than 30% TBSA.

NexoBrid (2 g/100 cm², corresponding to 0.02 g/cm²) was used as described in section 4.2.

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

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

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

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

The co-primary endpoints for the efficacy analysis were:

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

This 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

The following table shows results in mixed wounds. The comparisons in mixed wounds should be interpreted with caution since they are based on groups that are not fully randomized and the mixed wounds treated by NexoBrid were overall larger and had a larger full thickness area.

Mixed wounds (with partial and full-thickness area) requiring excision/dermabrasion (surgery)

	NexoBrid (Number of wounds)	SOC (Number of wounds)
% of wounds requiring surgery	41.7% (20/48)	78.3% (47/60)
% of wound area excised or dermabraded	25.5% (n=48)	64.0% (n=60)

Mixed wounds (with partial and full-thickness area) autografted

	NexoBrid (Number of wounds)	SOC (Number of wounds)
All mixed burns baseline characteristics	48 wounds	60 wounds
Size: % mean TBSA	7.43	6.33
Depth:		
Superficial (%TBSA)	0.67	0.92
DPT (% TBSA)	3.85	3.13
FT (% TBSA)	2.90	2.29
Incidence of autograft	70.8% (34/48)	63.3% (38/60)
% wound area autografted	55.5% (n=48)	45.8% (n=60)

The following table shows the time to complete wound closure from start of debridement.*

Wound Type	NexoBrid	SOC
	Days (mean ± SD) (Number of wounds)	Days (mean ± SD) (Number of wounds)
All wounds (ITT ¹)	30.5 ± 16.9 (154)	26.1 ± 16.0 (164)
Non-autografted wounds (ITT)	23.9 ± 13.0 (95)	24.5 ± 14.1 (85)
Autografted wounds (ITT)	41.0 ± 17.3 (59)	27.8 ± 17.7 (79)
Deep Partial Thickness wounds	26.6 ± 15.4 (101)	23.7 ± 13.6 (87)
Full Thickness wounds	31.9 ± 10.1 (7)	36.3 ± 26.0 (14)
Mixed wounds (deep partial and full thickness)	40.2 ± 17.1 (44)	27.7 ± 15.8 (59)
Non-autografted mixed wounds	29.5 ± 12.1 (11)	30.3 ± 15.5 (22)
Autografted mixed wounds	43.7 ± 17.3 (33)	26.2 ± 16.0 (37)

*These comparisons should be interpreted with caution since they are based on groups that are not fully randomized.

¹ ITT (Intent To Treat population): all randomized patients

The difference in time to complete wound closure is mainly related to the wound care strategy applied by the physician, where an attempt to minimise grafting and allow for spontaneous epithelialisation of the wound areas that still have dermis may prolong time to first autograft (time to autograft: NexoBrid: 14.7 days vs. SOC: 5.9 days) and hence prolong complete wound closure.

Paediatric population

Efficacy data generated in this study from a subgroup analysis for children and adolescents are summarised below. The available data are limited and NexoBrid 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 NexoBrid 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).

5.2 Pharmacokinetic properties

Absorption

The extent of systemic absorption from a burn wound, C_{max}, T_{max}, AUC, and t_{1/2} of bromelain from NexoBrid have been investigated in 16 burn patients with partial-thickness (mid- and deep-dermal) thermal burns. Average TBSA was 10%. 60% of the treated wounds area was partial thickness and/or

full thickness. NexoBrid was applied once to the burn wound at a dose of 2 g NexoBrid Powder/20 g gel/100 cm² of skin.

NexoBrid serum concentrations were determined using a modified sandwich electrochemiluminescence (ECL) immunoassay.

The range of total dose applied was 5 to 30 g concentrate of proteolytic enzymes enriched in bromelain from NexoBrid. In 4 patients, having received a dose of 5, 9, 12 and 17 g, respectively, there were indications of markedly higher systemic absorption.

C_{max} was 6020 ± 5020 ng/ml (mean ± SD) for the group of 15 patients, with a range of 888 to 15,700 ng/ml. In the 4 patients with indications of higher absorption, dose-normalised C_{max} ranged from 788-900 ng/ml per gram of NexoBrid. In the other patients, dose-normalised C_{max} ranged from 141-523 ng/ml per gram of NexoBrid.

A C_{max} of 40µg/ml may be possible in humans administered NexoBrid under licensed conditions, when it is considered that PK has only been evaluated in patients with largely superficial burns, receiving half the maximum dose.

The AUC from time zero to 48 hours after administration (AUC_{last}) was 43,400 ± 46,100 ngh/ml (mean ± SD) for the group of 15 patients, with a range of 4560-167,000 ngh/ml. In the patients with indications of higher absorption, dose-normalised (per gram of NexoBrid) AUC_{last} ranged from 4500-9820 ngh/ml per gram of NexoBrid. In the other patients, dose-normalised AUC_{last} ranged from 887-3930 ngh/ml per gram of NexoBrid.

These results for C_{max} and AUC_{last} indicate that systemic absorption may depend both on the applied NexoBrid dose (proportional to the covered wound area) and other, patient-specific factors.

T_{max} for 10 of the 15 patients was 2 hours and in 5 patients T_{max} was 4 hours.

Distribution

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

Elimination

Terminal half-life (determined using data from 16 to 48 hours post-dose for 12 patients) was 11.7 ± 3.5 hours (mean ± SD), with a range from 8.5 to 19.9 hours.

Paediatric population

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

5.3 Preclinical safety data

NexoBrid was well tolerated 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 dosage to 15% TBSA*) but higher doses were overtly toxic, causing haemorrhage in several tissues. Repeated intravenous injections of doses up to 12 mg/kg every third day in the mini-pig were well tolerated for the first three injections but severe clinical signs of toxicity (e.g. haemorrhages in several organs) were observed following the remaining three injections. Such effects could still be seen after the recovery period of 2 weeks.

In embryo-foetal development studies in rats and rabbits, intravenously administered NexoBrid revealed no evidence of indirect and direct toxicity to the developing embryo/foetus. However, maternal exposure levels were considerably lower than those maximally reported in clinical setting (10–500 times lower than human AUC, 3–50 times lower than the human C_{max}). Since NexoBrid was

poorly tolerated by the parent animals, these studies are not considered relevant for human risk assessment. 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

NexoBrid powder

Ammonium sulphate

Acetic acid

Gel

Carbomer 980

disodium phosphate anhydrous

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Topically applied medicinal products (such as silver sulfadiazine or povidone-iodine) at the wound site must be removed and the wound cleansed prior to NexoBrid application. Remaining antibacterial medicinal products may interfere with the activity of NexoBrid by decreasing its efficacy.

This medicinal product must not be mixed with other medicinal products.

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, angioedema, urticaria, and mucosal and gastrointestinal reactions. This should be considered when mixing NexoBrid powder with the gel. The powder should not be inhaled. See also section 4.4.

Accidental eye exposure must be avoided. In case of eye exposure, exposed eyes must be irrigated with copious amounts of water for at least 15 minutes. In case of skin exposure, NexoBrid must be rinsed off with water.

NexoBrid gel preparation (mixing powder with gel)

- The NexoBrid powder and gel are sterile. An aseptic technique must be used when mixing the powder with the gel.
- The vial with NexoBrid powder must be shaken vigorously to fragment the NexoBrid powder cake.
- 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. If necessary, a sterile spatula can be used to break the dry powder cake in its vial prior to transfer.
- 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
Eisenstrasse 5
65428 Rüsselsheim
Germany

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:

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**

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

Hälsa Pharma GmbH
Nikolaus-Dürkopp-Str. 4a
D-33602 Bielefeld
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

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs

The PSUR cycle for the medicinal product should follow the standard requirements until otherwise agreed by the CHMP.

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

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 NexoBrid receive a specific training and are provided with an Educational pack.

The MAH should undertake a controlled distribution of NexoBrid 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 NexoBrid. 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 NexoBrid

- The limitation of the total area than can be treated to 15% TBSA
- 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 NexoBrid

- 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 NexoBrid application
 - Protection of surrounding skin areas
- The method of preparation of NexoBrid and of its application to wound area

After applying NexoBrid

- The removal of NexoBrid and of dissolved eschar
 - The wound assessment and the warning against any repeat treatment
 - The wound management after NexoBrid 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 NexoBrid 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
- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH shall conduct a study on enzymatic debridement in burns patients (children and adults): A comparison to standard of care (protocol MW2010-03-02), based on a CHMP approved protocol.	31/12/2020

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

NexoBrid 2 g powder and gel for gel

Concentrate of proteolytic enzymes enriched in bromelain

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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).

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 2 g powder

1 bottle of 20 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
65428 Rüsselsheim
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/803/001

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

<Not applicable.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable.>

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

65428 Rüsselsheim

Germany

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

<Not applicable.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable.>

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

NexoBrid powder (vial)

1. NAME OF THE MEDICINAL PRODUCT

NexoBrid 2 g powder

Concentrate of proteolytic enzymes enriched in bromelain

2. STATEMENT OF ACTIVE SUBSTANCE

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).

3. LIST OF EXCIPIENTS

Excipients: Acetic acid, ammonium sulphate.

4. PHARMACEUTICAL FORM AND CONTENT

Powder
2 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 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
65428 Rüsselsheim
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/803/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

<Not applicable.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable.>

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

NexoBrid powder (vial)

1. NAME OF THE MEDICINAL PRODUCT

NexoBrid 5 g powder

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
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 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
65428 Rüsselsheim
Germany

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

<Not applicable.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable.>

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

Gel for NexoBrid powder

1. NAME OF THE MEDICINAL PRODUCT

Gel for NexoBrid 2 g

2. STATEMENT OF ACTIVE SUBSTANCE

Concentrate of proteolytic enzymes enriched in bromelain: 0.09 g/g (or 2 g/22 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
20 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

MediWound Germany GmbH
65428 Rüsselsheim
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/803/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

<Not applicable.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable.>

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

MediWound Germany GmbH
65428 Rüsselsheim
Germany

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

<Not applicable.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable.>

B. PACKAGE LEAFLET

Package leaflet: Information for the user

NexoBrid 2 g powder and gel for gel

Concentrate of proteolytic enzymes enriched in bromelain

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What NexoBrid is and what it is used for
2. What you need to know before NexoBrid is used
3. How NexoBrid is used
4. Possible side effects
5. How NexoBrid is stored
6. Contents of the pack and other information

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 adult patients 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 are allergic to bromelain
- if you are allergic to pineapples
- if you are allergic to papain
- if you 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 have a heart disease;
- you have a lung disease;
- your lung has been, or may have been damaged by inhalation of smoke;
-
- you are allergic to latex, bee stings, or olive tree pollen. If so, you 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 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 it less likely that you develop an allergic reaction to NexoBrid.

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

NexoBrid may reduce the ability of your blood to form clots, which increases the risk of bleeding. NexoBrid should be used with caution if you have a general tendency to bleed, a stomach ulcer, blood poisoning, or another condition that could cause you to bleed. After treatment with NexoBrid your doctor may check your 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, 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.

Children and adolescents

NexoBrid is not for use in patients younger than 18 years.

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.

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, rosiglitazone, repaglinide, tolbutamide and glipizide (used to treat diabetes),
 - paclitaxel and sorafenib (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 reaction to the cancer medicines fluorouracil and vincristine.
- cause an unwanted drop in blood pressure when you 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.

If you are not sure whether you 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.

2 g NexoBrid powder mixed in 20 g gel is applied to a burn wound area of 100 cm².

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% (one eighth) 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 will be given appropriate medicine to prevent and treat pain at least 15 minutes before NexoBrid is applied.
- 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 NexoBrid powder, gel bottle, and the prepared NexoBrid gel should only be used for one patient.

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 notice any of these symptoms or signs, inform your doctor or caregiver immediately.

Very common side effects (may affect more than 1 in 10 people)

- Fever

Common side effects (may affect up to 1 in 10 people)

- Pain (even if medicines are used to prevent or lessen pain caused by the removal of burnt tissue)
- Infection of the burn wound
- Complications of the wound including; wound opening, wounds drying out and breaking down and failure of skin grafts to heal properly

Reporting of side effects

If you 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: 2 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 (2 g) and gel in a bottle (20 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.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

MediWound Germany GmbH

Eisenstrasse 5

65428 Rüsselsheim

Germany

Manufacturer:

Hälsa Pharma GmbH

Nikolaus-Dürkopp-Str. 4a

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in <{MM/YYYY}> <{month YYYY}.>

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.
- 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 interfere with the activity of NexoBrid by decreasing its efficacy.
- The area from which you wish to remove the eschar must be surrounded with a sterile paraffin ointment adhesive barrier by applying it a few centimetres outside of the treatment area (using a dispenser). The paraffin layer must not come into contact with the area to be treated 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, such areas can be protected by a layer of a sterile fatty ointment.
- 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.
- The vial with NexoBrid powder must be shaken vigorously to fragment the NexoBrid powder cake.
- 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. If necessary, a sterile spatula can be used to break the dry NexoBrid powder cake in its vial prior to transfer.
- 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

- 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

- Appropriate preventive analgesia medicinal products must be administered.
- After 4 hours of NexoBrid treatment, the occlusive dressing must be removed using aseptic techniques.
- The adhesive barrier must be removed using a sterile blunt-edged instrument (e.g., tongue depressor).
- The dissolved eschar must be removed from the wound by wiping it away with a sterile blunt-edged instrument.
- The wound must be wiped thoroughly first with a large sterile dry gauze or napkin, followed by a sterile gauze or napkin that has been soaked with sterile isotonic sodium chloride 9 mg/ml (0.9%) solution. The treated area must be rubbed until the appearance of a pinkish surface with bleeding points or a whitish tissue. Rubbing will not remove adhering undissolved eschar in areas where the eschar still remains.
- A dressing soaked with an antibacterial solution 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.

Recommendations for safe handling

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, angioedema, urticaria, and mucosal and gastrointestinal reactions. This should be considered when mixing NexoBrid powder with the gel. In NexoBrid, the powder containing the concentrate of proteolytic enzymes enriched in bromelain is present in the form of a sterile lyophilised cake, reducing the likelihood of inhalational exposure.

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.

Disposal

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

Package leaflet: Information for the user

NexoBrid 5 g powder and gel for gel

Concentrate of proteolytic enzymes enriched in bromelain

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What NexoBrid is and what it is used for
2. What you need to know before NexoBrid is used
3. How NexoBrid is used
4. Possible side effects
6. How NexoBrid is stored
6. Contents of the pack and other information

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 adult patients 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 are allergic to bromelain
- if you are allergic to pineapples
- if you are allergic to papain
- if you 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 have a heart disease;
- you have a lung disease;

- your lung has been, or may have been damaged by inhalation of smoke;
-
- you are allergic to latex, bee stings, or olive tree pollen. If so, you 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 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 it less likely that you develop an allergic reaction to NexoBrid.

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

NexoBrid may reduce the ability of your blood to form clots, which increases the risk of bleeding. NexoBrid should be used with caution if you have a general tendency to bleed, a stomach ulcer, blood poisoning, or another condition that could cause you to bleed. After treatment with NexoBrid your doctor may check your 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, 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.

Children and adolescents

NexoBrid is not for use in patients younger than 18 years.

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.

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, rosiglitazone, repaglinide, tolbutamide and glipizide (used to treat diabetes),
- paclitaxel and sorafenib (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 reaction to the cancer medicines fluorouracil and vincristine.
- cause an unwanted drop in blood pressure when you 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.

If you are not sure whether you 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 to a burn wound area of 250 cm².

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% (one eighth) 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 will be given appropriate medicine to prevent and treat pain at least 15 minutes before NexoBrid is applied.
- 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 NexoBrid powder, gel bottle, and the prepared NexoBrid gel should only be used for one patient.

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 notice any of these symptoms or signs, inform your doctor or caregiver immediately.

Very common side effects (may affect more than 1 in 10 people)

- Fever

Common side effects (may affect up to 1 in 10 people)

- Pain (even if medicines are used to prevent or lessen pain caused by the removal of burnt tissue)
- Infection of the burn wound
- Complications of the wound including; wound opening, wounds drying out and breaking down and failure of skin grafts to heal properly

Reporting of side effects

If you 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: 5 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 infections.

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.

Marketing Authorisation Holder and Manufacturer

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Eisenstrasse 5

65428 Rüsselsheim

Germany

Manufacturer:

Hälsa Pharma GmbH

Nikolaus-Dürkopp-Str. 4a

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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.
- 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 interfere with the activity of NexoBrid by decreasing its efficacy.
- The area from which you wish to remove the eschar must be surrounded with a sterile paraffin ointment adhesive barrier by applying it a few centimetres outside of the treatment area (using a dispenser). The paraffin layer must not come into contact with the area to be treated 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, such areas can be protected by a layer of a sterile fatty ointment.
- 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.
- The vial with NexoBrid powder must be shaken vigorously to fragment the NexoBrid powder cake.
- 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. If necessary, a sterile spatula can be used to break the dry NexoBrid powder cake in its vial prior to transfer.
- 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

- 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

- Appropriate preventive analgesia medicinal products must be administered.
- After 4 hours of NexoBrid treatment, the occlusive dressing must be removed using aseptic techniques.

- The adhesive barrier must be removed using a sterile blunt-edged instrument (e.g., tongue depressor).
- The dissolved eschar must be removed from the wound by wiping it away with a sterile blunt-edged instrument.
- The wound must be wiped thoroughly first with a large sterile dry gauze or napkin, followed by a sterile gauze or napkin that has been soaked with sterile isotonic sodium chloride 9 mg/ml (0.9%) solution. The treated area must be rubbed until the appearance of a pinkish surface with bleeding points or a whitish tissue. Rubbing will not remove adhering undissolved eschar in areas where the eschar still remains.
- A dressing soaked with an antibacterial solution 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.

Recommendations for safe handling

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, angioedema, urticaria, and mucosal and gastrointestinal reactions. This should be considered when mixing NexoBrid powder with the gel. In NexoBrid, the powder containing the concentrate of proteolytic enzymes enriched in bromelain is present in the form of a sterile lyophilised cake, reducing the likelihood of inhalational exposure.

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.

Disposal

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

Annex IV

Grounds for one additional renewal

Grounds for one additional renewal

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of NexoBrid remains positive, but considers that its safety profile is to be closely monitored for the following reasons.

An imposed additional pharmacovigilance study is ongoing, the results of which are expected to yield important new safety data which could impact on the benefit-risk balance of the product. The MAH is conducting a study on enzymatic debridement in burns patients (children and adults), a comparison to standard of care (protocol MW2010-03-02).

The CHMP requested data generation through a clinical study to confirm the absence of a direct negative impact of NexoBrid debridement on the initial time to complete wound closure and possibly associated adverse events.

Therefore, based upon the safety profile of NexoBrid the CHMP concluded that the MAH should submit one additional renewal application in 5 years.