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 cm^2.

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 and possible bleeding from the wound bed, acute wound areas such as lacerations or escharotomy incisions should be protected by a layer of a sterile fatty ointment or fatty dressing (e.g. petrolatum gauze)..
- Sterile isotonic sodium chloride 9 mg/ml (0.9%) solution must be sprinkled on the burn wound. The wound must be kept moist during the application procedure.

NexoBrid application

- Within 15 minutes of mixing, 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, angiooedema, 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 (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).

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

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 cm^2, corresponding to 0.02 g/cm^2) 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)

*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 $t_{½}$ 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 cm^2 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 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 ± 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, angiooedema, urticaria, and mucosal and gastrointestinal reactions. This should be considered when mixing NexoBrid powder with the gel. The powder should not be inhaled.. See also section 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 powder vial must be opened by carefully tearing off the aluminium cap and removing the rubber stopper.
- When opening the gel bottle, it must be confirmed that the tamper-evident ring is separating from the bottle's cap. If the tamper-evident ring was already separated from the cap before opening, the gel bottle must be discarded and another, new gel bottle used.
- The powder is then transferred into the corresponding gel bottle.
- Powder and gel must be mixed thoroughly until a uniform, slightly tan to slightly brown mixture is obtained. This usually requires mixing the powder and the gel for 1 to 2 minutes.
- The gel should be prepared at the patient's bedside.

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

7. MARKETING AUTHORISATION HOLDER

MediWound Germany GmbH
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: 10.11.2017

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.