swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

NexoBrid

International non-proprietary name:	concentrate of proteolytic enzymes enriched in bromelain
Pharmaceutical form:	powder and gel for gel
Dosage strength(s):	0.09 g/g
Route(s) of administration:	topical use
Marketing authorisation holder:	Triskel INTEGRATED SERVICES SA
Marketing authorisation no.:	68012
Decision and decision date:	extension of therapeutic indication approved on 24 July 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DPT	Deep partial thickness
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FT	Full thickness
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SOC	Standard of care
SPT	Superficial partial thickness
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TBSA	Total body surface area

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 29 September 2020.

2.2 Indication and dosage

2.2.1 Requested indication

NexoBrid is indicated in all age groups for removal of eschar in patients with deep partial- and full-thickness thermal burns.

2.2.2 Approved indication

NexoBrid is indicated in all age groups for removal of eschar in patients with deep partial- and full-thickness thermal burns.

2.2.3 Requested dosage

Summary of the requested standard dosage:

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

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	21 May 2024
Formal objection	13 June 2024
Response to formal objection	11 August 2024
Formal control completed	3 September 2024
List of Questions (LoQ)	19 December 2024
Response to LoQ	17 February 2025
Preliminary decision	24 April 2025
Response to preliminary decision	16 June 2025
Final decision	24 July 2025
Decision	approval

3 Medical context

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

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

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

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

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

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

4 Nonclinical aspects

The nonclinical documentation submitted supports the approval of NexoBrid for the applied indication extension in the paediatric population. A juvenile repeated-dose toxicity study to evaluate the potential toxicity and toxicokinetics of the test article in juvenile farm pigs (28 to 36 days old on Day 1), covering children of two years of age, has been submitted. The results of this study were consistent with those previously obtained in adolescent and adult (mini)pigs from single- and repeated-dose intravenous studies. The findings from this juvenile toxicity study support the extension of the indication to the paediatric population, with no additional safety risks identified.

Based on the Environmental Risk Assessment (ERA), there is no significant risk to the environment.

The Risk Management Plan (RMP) adequately addresses the nonclinical findings and their relevance to clinical use.

From a nonclinical perspective, there are no objections to the approval of the proposed indication extension.

5 Clinical aspects

The evaluation of the clinical efficacy, safety and pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA. The available assessment report and respective product information from EMA (Procedure No. EMEA/H/C/002246/II/0058) was used as a basis for the clinical efficacy, safety and pharmacology evaluation.

For further details concerning clinical efficacy, safety, pharmacology and dosing recommendations, see section 7 (Appendix) of this report.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for NexoBrid was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

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

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

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

NexoBrid 5 g

Composition

Active substances

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

Excipients

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

Pharmaceutical form and active substance quantity per unit

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

Indications/Uses

NexoBrid is indicated in all age groups for the removal of eschar in patients with deep partial- and full-thickness thermal skin burns.

Dosage/Administration

NexoBrid should only be applied by a qualified healthcare professional in a centre specialising in burn care.
Adults

2 g of powder in 20 g of gel are applied to 1% of the Total Body Surface Area (TBSA) of an adult, which corresponds to approximately 180 cm^2, with a gel layer thickness of 1.5 to 3 mm.
5 g of powder in 50 g of gel are applied to 2.5% of the TBSA, which corresponds to approximately 450 cm^2 for an adult, with a gel layer thickness of 1.5 to 3 mm.
NexoBrid should not be applied to more than 15% of the TBSA (see "Warnings and Precautions: Coagulopathy").

Paediatric population

Children and adolescents (from birth to 18 years of age)

In paediatric patients aged 4 to 18 years, NexoBrid should not be applied to more than 15% of the TBSA.
In paediatric patients aged 0 to 3 years, this medicinal product should not be applied to more than 10% of the TBSA.
NexoBrid should remain in contact with the burn for a duration of 4 hours. Information on the use of NexoBrid on areas where eschar remained after the first application is very limited. A second application is not recommended.

Traceability

To ensure the traceability of biological medicinal products, the trade name and batch number should be documented for each treatment.

Patients with hepatic impairment

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

Patients with renal impairment

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

Elderly patients

Clinical data on NexoBrid in elderly patients (> 65 years) are limited. The benefit/risk assessment in elderly patients should take into account the higher frequency of concomitant disease or other drug treatment. No dosage adjustment is necessary.

Method of administration

Cutaneous route.
Before use, the powder must be mixed with the gel to produce a uniform gel. For instructions on preparing NexoBrid gel, see the section "Special instructions/Handling instructions".
NexoBrid should be applied to a moist, keratin-free (blisters removed) and clean wound. Each vial, gel or reconstituted gel of NexoBrid should only be used for one patient.

Before applying NexoBrid, topical medications (such as silver sulfadiazine or povidone-iodine) applied to the wound site must be removed and the wound must be cleaned, as medication-saturated eschar and medication residues reduce the activity of the gel and decrease its effectiveness.

Preparation of the patient and the wound area

The total wound surface area treated with NexoBrid must not exceed 15% of the TBSA (see also section "Warnings and precautions, Coagulopathy").

- Enzymatic debridement is a painful procedure and requires adequate analgesia and/or anaesthesia. Pain management should be initiated at least 15 minutes before applying NexoBrid, as with any major dressing change.
- The wound must be thoroughly cleaned and the superficial keratin layer or blisters must be removed from the wound area; otherwise, the keratin would prevent the eschar from coming into direct contact with NexoBrid, which would block the action of NexoBrid.
- A compress impregnated with an antibacterial solution (e.g. chlorhexidine or sodium hypochlorite (Dakin's solution) at 0.05-0.5%, hypertonic saline solution at 5-10%) should be applied for 2 hours. Silver sulfadiazine or povidone-iodine should not be used.
- All topical antibacterial medicines must be removed before applying NexoBrid. If antibacterial medicines remain, they may reduce the activity of NexoBrid and decrease its effectiveness.
- The area where the eschar is to be removed should be surrounded by an insulating layer of sterile paraffin-based ointment, applying it a few centimetres away from the treatment area (using a tube). The paraffin layer must not come into contact with the area to be treated to prevent the eschar from being covered, which would prevent it from coming into direct contact with NexoBrid. To prevent possible irritation of abraded skin through accidental contact with NexoBrid, and possible bleeding from the wound area, areas of the wound at risk, such as lacerations or escharotomy incisions, should be protected with a layer of sterile ointment or an ointment dressing (e.g. gauze with Vaseline).
- The burn should be irrigated with a sterile isotonic sodium chloride solution of 9 mg/ml (0.9%). The wound should remain moist during application.

Application of NexoBrid

- Moisten the area to be treated by sprinkling sterile saline solution onto the area delimited by the fatty ointment adhesive barrier.
- Within 15 minutes of preparation (see "Other Information, Instructions for handling"), a layer of NexoBrid 1.5 to 3 millimetres thick should be applied locally to the moistened wound.
- The wound should then be covered with a sterile occlusive film that adheres to the insulating layer of sterile ointment applied as described above (see “Preparation of the patient and the wound area”). The entire occlusive dressing should be impregnated with NexoBrid gel, and particular care should be taken to ensure that no air is trapped under the dressing. Applying light pressure to the occlusive dressing where it contacts the insulating layer of paraffin will ensure

good adhesion between the occlusive film and the insulating layer, and will keep NexoBrid in place on the treatment area.
- The dressed wound should be covered with a thick, soft, flexible dressing, secured with a bandage.
- The dressing should remain in place for 4 hours.

Removal of NexoBrid
- Removal of this medicinal product is a painful procedure and therefore requires adequate analgesia and/or anaesthesia. Appropriate analgesics should be administered preventively at least 15 minutes before removal of the gel.
- After 4 hours of treatment with NexoBrid, the occlusive dressing should be removed using aseptic techniques.
- The insulating layer of paraffin must be removed using a sterile instrument with rounded edges (e.g., a tongue depressor).
- The dissolved eschar must be removed from the wound using a sterile instrument with rounded edges.
- The wound should first be wiped thoroughly with a large piece of sterile dry gauze or compress, then with sterile gauze or compress that has been soaked in sterile isotonic sodium chloride solution at 9 mg/ml (0.9%). The treated area should be rubbed until a pinkish surface with haemorrhagic spots or whitish tissue appears. Rubbing will not remove any undissolved eschar that is still adhering.
- A compress impregnated with an antibacterial solution (e.g. chlorhexidine or sodium hypochlorite (Dakin's solution) at 0.05-0.5%, hypertonic saline solution at 5-10%) should be applied for a further 2 hours.

Burn care after debridement
- The debrided area must be immediately covered with temporary or permanent skin substitutes or dressings to prevent drying and/or the formation of a pseudo-escar and/or infection.
- Before applying a permanent skin covering or temporary skin substitute to an area that has recently been debrided with enzymes, a wet-to-dry dressing should be applied.
- Before applying grafts or primary dressings, the debrided wound should be cleaned, for example by brushing or scraping, to allow the dressing to adhere.
- Wounds with areas of third-degree burns and deep burns should receive an autograft as soon as possible after debridement. Special care should be taken if permanent skin coverings (e.g. autografts) are applied to second-degree wounds shortly after debridement (see section "Warnings and precautions").

Contraindications

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

Warnings and precautions

Burns for which NexoBrid is not recommended

The use of NexoBrid is not recommended in the following cases:

- penetrating burns involving a device (e.g. implants, pacemakers and shunts) and/or vital areas (e.g. arteries, eyes) that are or may be exposed during debridement;
- chemical burns;
- application in cavities such as the peritoneal and pleural cavities;
- burns contaminated with radioactive or other hazardous substances to avoid unpredictable reactions with the product and the increased risk of dispersion of the toxic substance;
- foot burns in diabetic patients and patients with venous occlusive disease;
- electrical burns.

Systemic absorption

A concentrate of proteolytic enzymes enriched in bromelain is absorbed systemically from burns (see section "Pharmacokinetics").

Pharmacokinetic data on patients with burns covering more than 15% of the total body surface area (TBSA) are limited. For safety reasons (see also section "Warnings and precautions, Coagulopathy"), this medicine should not be applied to more than 15% of the TBSA in adults and paediatric patients aged 4 to 18 years.

In paediatric patients aged 0 to 3 years, this medicine should not be applied to more than 10% of the TBSA.

Use in patients with cardiopulmonary and pulmonary disease

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

Use in patients with varicose veins

This medicine should be used with caution on areas with varicose veins to avoid erosion of the vein wall and the risk of bleeding.

Burns for which there is little or no experience

There are no data on the use of NexoBrid on perineal and genital burns. *Information on the use of NexoBrid is limited in cases of facial burns.* The literature reports the successful use of NexoBrid on facial burns. Burn surgeons with no experience in using this medicine should not start using it on facial burns. In these patients, NexoBrid should be used with caution. The eyes must be carefully protected during the treatment of facial burns by applying a greasy ophthalmic ointment to the eyes and a vaseline ointment around the eyes to act as a skin protector, isolating and covering the eyes with an occlusive film.

Prevention of wound complications

The general principles of burn care should be followed when using NexoBrid. This means, in particular, covering the wound well to protect the exposed tissue (see section "Dosage/method of use").
During studies on NexoBrid, spontaneous epithelialisation healing was attempted on wounds with visible dermal remnants. In several cases, adequate healing could not be achieved, requiring subsequent autografting and resulting in delayed healing, which may be associated with an increased risk of wound complications. Therefore, wounds with areas of third-degree burns and deep burns should receive an autograft as soon as possible after debridement with NexoBrid (see study results in the "Clinical Efficacy" section). Special care should be taken if permanent skin coverings (e.g. autografts) are applied to second-degree burns shortly after debridement with NexoBrid (see also sections "Dosage/administration" and "Adverse effects").
As with surgical debridement of the wound, the debrided area must be immediately covered with temporary or permanent skin substitutes or dressings to prevent drying and/or the formation of a pseudo-escar and/or infection. When applying a permanent skin covering (e.g. autograft) or a temporary skin substitute (e.g. allograft) to an area recently debrided by enzymes, care must be taken to clean the debrided wound, for example by brushing or scraping, to allow the dressing to adhere.
Eye protection
Direct contact with the eyes must be avoided. If there is a risk of eye contact, the patient's eyes must be protected with a greasy ophthalmic ointment.
In case of eye exposure, rinse the exposed eyes with plenty of water for at least 15 minutes. An ophthalmological examination is recommended before and after debridement.
Hypersensitivity reactions, skin exposure, inhalation
The potential of NexoBrid (a protein-based product) to cause sensitisation should be taken into account when patients are subsequently re-exposed to products containing bromelain. The use of NexoBrid on subsequent burns is not recommended.
Serious allergic reactions have been reported, including anaphylactic reactions (with manifestations including rash, erythema, hypotension, tachycardia) in patients who have undergone debridement with NexoBrid (see section "Adverse reactions"). In these cases, a causal relationship with NexoBrid was considered possible, although a relationship with concomitant medications could not be ruled out.
Allergic reactions to inhaled bromelain have been reported in the literature (including anaphylactic reactions and other immediate reactions with manifestations such as bronchospasm, angioedema, urticaria, and mucosal and gastrointestinal reactions). A study evaluating the amount of airborne particles during the preparation of NexoBrid gel revealed no occupational risk. However, appropriate measures when handling the debriding agent (including wearing gloves, protective gown and protective mask) are required.
A history of allergies should be established before administering the medicine (see sections "Contraindications" and "Handling precautions").

In case of skin exposure, NexoBrid should be rinsed off with water to reduce the risk of skin sensitisation (see section "Handling precautions").

Cross-reactivity

Cross-allergy between bromelain and papaya/papain, latex proteins (latex-fruit syndrome), bee venom and olive pollen has been reported in the literature.

Analgesia

Enzymatic debridement is a painful procedure and should therefore only be performed after adequate analgesia and/or anaesthesia has been administered.

Coagulopathy

A reduction in platelet aggregation and plasma fibrinogen levels and a moderate increase in activated partial thromboplastin time and prothrombin time have been reported in the literature as possible effects after oral administration of bromelain. Data obtained *in vitro* and in animals suggest that bromelain may also activate fibrinolysis. During the clinical development of NexoBrid, there was no evidence of an increased tendency to bleed, nor was there any bleeding at the debridement site. The treatment should not be used in patients with uncontrolled coagulation disorders. NexoBrid should be used with caution in patients receiving anticoagulant therapy or other drugs affecting coagulation and in patients with low platelet counts and a high risk of haemorrhage due to other causes such as peptic ulcers and septicaemia.

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

Monitoring

In addition to the usual monitoring of burn patients (e.g., vital signs, blood volume, fluid/electrolyte balance, complete blood count, serum albumin and liver enzyme levels), patients treated with NexoBrid should be monitored for:

- Increased body temperature.
- Signs of local and systemic infectious and inflammatory processes.
- Clinical situations that could be aggravated by analgesic premedication (e.g., stomach distension, nausea and risk of sudden vomiting, constipation) or antibiotic prophylaxis (e.g., diarrhoea).
- Signs of local or systemic allergic reactions.
- Possible effects on haemostasis (see above).

Removal of topical antibacterial agents prior to application of NexoBrid

All topical antibacterial medicinal products must be removed before applying NexoBrid. Remaining antibacterial medicinal products reduce the activity of NexoBrid by decreasing its efficacy.

Interactions

No interaction studies with NexoBrid have been performed.

Medicinal products affecting coagulation

A reduction in platelet aggregation and plasma fibrinogen levels, as well as a moderate increase in activated partial thromboplastin time and prothrombin time, have been reported as possible effects following oral administration of bromelain. Data obtained *in vitro* and in animals suggest that bromelain may also activate fibrinolysis. Special attention and monitoring are therefore required when prescribing concomitant medication that affects coagulation (see also section "Warnings and precautions").

CYP2C8 and CYP2C9 substrates

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

Topical antibacterial medicinal products

Topical antibacterial medicinal products (e.g. silver sulfadiazine or povidone iodine) may reduce the effectiveness of NexoBrid (see section "Warnings and precautions").

Fluorouracil and vincristine

Bromelain may increase the action of fluorouracil and vincristine. These patients should be closely monitored for increased toxicity.

ACE inhibitors

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

Benzodiazepines, barbiturates, narcotics and antidepressants

Bromelain may increase the drowsiness induced by certain medications (e.g., benzodiazepines, barbiturates, narcotics, and antidepressants). This should be taken into account when determining dosage.

Pregnancy, lactation

Pregnancy

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

Animal studies are insufficient to properly assess the ability of NexoBrid to affect embryonic/foetal development (see section "Preclinical data").

As the safe use of NexoBrid during pregnancy has not yet been established, NexoBrid is not recommended during pregnancy.

Lactation

It is not known whether concentrate of proteolytic enzymes enriched in bromelain or its metabolites are excreted in breast milk. A risk to newborns/infants cannot be excluded. Breastfeeding should be discontinued for at least 4 days from the start of NexoBrid application.

Fertility

No studies have been conducted to assess the effects of NexoBrid on fertility.

Effects on ability to drive and use machines

Not relevant.

Undesirable effects

During the clinical development programme, 536 patients were treated with NexoBrid in 9 clinical studies, including 3 open-label, randomised, controlled phase 3 studies.
The most frequently reported adverse reactions in the pooled adult population of the MW2004, MW2005, MW2008 and MW2010 studies in the arm treated with this medicinal product (203 patients in total) were nausea (reported in 13.3% of patients treated with NexoBrid) and pain (3.9%).
The most frequently reported adverse reactions in the pooled paediatric population (0-18 years) (89 patients in total) in the MW2004, MW2008 and MW2012 studies in the arm treated with this medicinal product were pyrexia and pain (incidence of 16.9% and 7.9%, respectively).
Serious adverse reactions by preferred term, occurring in more than one patient (≥ 1.1%), were: septicaemia and bacterial wound infection.
Adverse reactions up to 3 months after wound healing are detailed below.
The following definitions apply to the frequency terminology used below:
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).
Frequency unknown (cannot be estimated from the available data)
The frequencies of adverse effects presented below reflect the use of NexoBrid to remove eschar from deep second-degree or third-degree burns as part of a protocol with local antibiotic prophylaxis, recommended analgesia/anaesthesia and wound protection after application of NexoBrid for 4 hours with an occlusive dressing to keep NexoBrid in place on the wound.
Infections and infestations
Common: wound infection including cellulitis
Immune system disorders
Common: non-serious allergic reactions such as rash

Frequency not known: severe allergic reactions including anaphylactic reactions

Cardiac disorders

Common: tachycardia

Skin and subcutaneous tissue disorders

Common: wound complications (including wound desiccation, wound aggravation, wound reopening, graft loss/rejection), local rash, local pruritus

Uncommon: intradermal haematoma

General disorders and administration site conditions

Very common: pyrexia/hyperthermia

Common: local pain

Description of selected undesirable effects

Immunogenicity

In the DETECT study, immunogenicity tests were performed on samples taken before and after treatment with NexoBrid (before treatment, day 28, day 56, 6 months and 24 months).

Prior to treatment, 39.4% (26/66) of subjects tested were positive for NexoBrid antibodies, which may reflect prior sensitisation to pineapple-derived proteins and glycoproteins carrying cross-reactive carbohydrate determinants. The incidence of antibodies appearing during treatment was 92.4% (61/66), divided between 62.3% (38/61) of subjects who were negative at baseline and 37.7% (23/61) of subjects who were positive at baseline and had at least a fourfold increase in antibody titres after treatment.

The timing of antibody development during treatment (increase in antibody titres) was consistent with an immune response through affinity maturation to a xenogeneic protein (100% seroconversion at 4 weeks), and the response was persistent (at least 24 months).

There was no apparent relationship between the maximum antibody titre after treatment and the total dose of NexoBrid (in grams) or between the maximum antibody titre after treatment and the treated TBSA. There was no apparent relationship between efficacy (complete elimination of eschar) and antibody titre before or after treatment. No clear relationship could be established between the presence of antibodies prior to treatment and the incidence of hypersensitivity reactions.

Paediatric population

Clinical trial data in paediatric patients (from birth to 18 years of age) include the use of this medicine in a controlled study against SOC (MW2012), in which 69 patients were exposed to this medicine (age range: from birth to 18 years; see section "Clinical efficacy" for age distribution), and use in paediatric patients in studies MW2004 and MW2008, which included 17 and 3 paediatric patients, respectively (age range: 4-17 years).

Overall, the safety profile in paediatric patients is similar to that in adults. Given the small number of adverse events reported in each age group, it is not possible to draw valid conclusions regarding possible age-related differences in the safety profile.

Reporting suspected side effects

The reporting of suspected side effects after authorisation is of great importance. It allows for continuous monitoring of the benefit-risk ratio of the medicine. Healthcare professionals are required to report any suspected new or serious side effects via the ElViS (Electronic Vigilance System) online reporting portal. Information on this can be found at www.swissmedic.ch.

Overdose

In a clinical study, the treatment of patients with deep second-degree and/or third-degree burns with a concentrate of proteolytic enzymes enriched in bromelain prepared in a powder:gel of 1:5 (0.16 g per g of mixed gel) did not produce significantly different safety results compared to treatment with a concentrate of proteolytic enzymes enriched in bromelain prepared in a powder:gel ratio of 1:10 (0.09 g per 1 g of prepared gel).
Limited data from clinical trials and post-marketing use of NexoBrid at a concentration of 0.09 g per 1 g of mixed gel did not indicate an increased risk when 2 applications of NexoBrid were used on a TSBA > 15% (up to 30% TSBA).

Properties/Effects

ATC code

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

Mechanism of action/Pharmacodynamics

The concentrate of proteolytic enzymes enriched in bromelain is a locally applied debriding agent for removing eschar from second-degree and third-degree burns.
The enzyme mixture contained in NexoBrid dissolves burn eschar. The specific components responsible for this effect have not been identified. The main component is bromelain from pineapple stems.

Clinical efficacy

The efficacy and safety of NexoBrid for the debridement of deep partial-thickness and full-thickness thermal skin burns were evaluated in three pivotal Phase 3, multicentre, randomised, controlled studies (MW2010, MW2004 and MW2012).
DETECT study (MW2010) – Phase 3b
This was a randomised, controlled, assessor-blinded, three-arm study comparing NexoBrid, the standard of care (SOC) and an gel vehicle (placebo) in adult hospitalised patients with deep partial-thickness and full-thickness thermal burns covering 3 to 30% of the total body surface area (TBSA) without exceeding 30% of the TBSA.

A total of 175 patients were randomised (intention-to-treat population) in a 3:3:1 ratio (NexoBrid: SOC: gel vehicle), and 169 patients received treatment. Patients in the SOC arm were treated with surgical and/or non-surgical SOC, at the investigator's discretion.
Demographic data and baseline wound characteristics were generally comparable across arms. Patient ages ranged from 18 to 75 years in the NexoBrid arm, 18 to 72 years in the SOC arm, and 18 to 70 years in the gel vehicle arm. The mean age in the three arms was 41 years, and the percentage of male patients was 65% in the NexoBrid arm, 79% in the SOC arm, and 60% in the placebo arm. The target wound (TW) corresponded to the surface of the burn to be treated (eschar removal) with NexoBrid, SOC, or placebo. The mean percentage of TBSA of TWs was 6.28% for patients in the NexoBrid arm, 5.91% for the SOC arm, and 6.53% for the gel vehicle arm (mean of 1.7 TWs per subject).
The primary endpoint was the incidence of complete (> 95%) eschar removal with NexoBrid compared to the gel vehicle. Secondary endpoints comparing NexoBrid to the SOC included the time to complete eschar removal, the incidence of surgical excision, and blood loss associated with debridement. Time to complete wound healing, long-term cosmesis and functional outcome measured using the Modified Vancouver Scale (MVSS) after the 12 months follow-up period were analysed as safety endpoints.
The study results show that the incidence of complete eschar removal was significantly higher in the NexoBrid arm than in the gel vehicle arm.

Incidence of complete eschar removal (DETECT study)

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

ER = eschar remouval

Compared to the SOC, NexoBrid resulted in statistically significant reductions in the incidence of surgical eschar removal (tangential/minor excision/avulsion/Versajet and/or dermabrasion), the median time to complete eschar removal, and blood loss associated with eschar removal (see table below).

Incidence of surgical excision of eschar, time to complete eschar removal, and blood loss (DETECT study)

	NexoBrid (N=75)	SOC (N=75)	p-value
Incidence of surgical debridement (number of subjects)	4.0% (3)	72.0% (54)	p < 0.0001
Median time to complete debridement of the eschar	1.0 day	3.8 days	p < 0.0001
Blood loss associated with the eschar removal[a]	14.2 ± 512.4 mL	814.5 ± 1020.3 mL	p < 0.0001

[a] Actual blood loss was calculated using the method described by McCullough in 2004:

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

Where EBV = estimated blood volume at 70 cm³/kg*body weight (kg); (Hb_{before}- Hb_{after}) = change in haemoglobin level during the eschar removal process; V_{WB} =Volume [mL] of total blood volume transfused during the eschar removal process; V_{PC}= Volume [mL] of red blood cell concentrate transfused during the eschar removal process.

Long-term results (12 and 24 months after wound healing)

The phase 3 study (DETECT) included long-term follow-up to assess cosmesis and functional aspects at 12- and 24-month follow-up visits. After 12 months, assessment of the scar using the Modified Vancouver Scar Score (MVSS) showed comparable results between the different treatments NexoBrid, SOC, and gel vehicle with respective mean scores of 3.70, 5.08, and 5.63. At 24 months, the mean MVSS scores were 3.04, 3.30 and 2.93, respectively. Statistical analyses showed the non-inferiority (non-inferiority margin of 1.9 points) of NexoBrid treatment compared to SOC, and showed that NexoBrid treatment has no clinically significant deleterious effect on the cosmesis and functional status of the burn scar compared to SOC 24 months after wound healing.
Functionality and quality of life (QoL) measurements at 12 and 24 months were similar between the different treatment groups. Mean scores on the Lower Extremity Functional Scale (LEFS), average QuickDASH scores, range of motion (ROM) assessments, and long-term QoL, measured using the EQ-5D visual analogue scale (VAS) and the BSHS-B (Burn Specific Health Scale-Brief), were similar across the different treatment groups.

MW2004 Study – Phase 3

The MW2004 study was a Phase 3, randomised, multicentre, multinational, open-label validation study comparing NexoBrid with SOC in hospitalised patients with deep partial-thickness and full-thickness thermal burns covering 5 to 30% of the TBSA, not exceeding 30% of the TBSA. The mean burn area, as a percentage of the BSA, was 5.1 ± 3.5 for this medicinal product and 5.2 ± 3.4 for the SOC.
The SOC consisted of primary surgical excision and/or non-surgical debridement using topical medications to induce maceration and autolysis of the eschar, depending on the standard practice at each study site.

The age range of the NexoBrid arm was 4.4 to 55.7 years. The age range of the SOC arm was 5.1 to 55.7 years.

The effectiveness of eschar removal was assessed by determining the percentage of wound area where eschar remained and required additional intervention by excision or dermabrasion, and the percentage of wounds requiring surgical removal.

The effect on eschar removal time was assessed in patients whose eschar was successfully removed (with at least 90% of the eschar in all wounds of a given patient removed) by determining the time between injury, as well as informed consent, and actual removal.

The co-primary endpoints for efficacy analysis were:

- the percentage of second-degree wounds (deep partial-thickness thermal burns) requiring excision or dermabrasion, and
- the percentage of second-degree wounds (deep partial-thickness thermal burns) that received an autograft.

This endpoint can only be assessed for deep second-degree wounds without third-degree burn areas, as the latter always require grafting.

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

	NexoBrid	SOC	p-value
Second-degree burns requiring excision/dermabrasion (surgical intervention)			
Number of wounds	106	88	
% of wounds requiring surgical intervention	15.1%	62.5%	<0.0001
% of wound area excised or dermabraded[1] (mean ± standard deviation)	5.5% ± 14.6	52.0% ± 44.5	<0.0001
Deep partial-thickness second-degree burns treated with autograft*			
Number of wounds	106	88	
% of wounds autografted	17.9%	34.1%	0.0099
% of wound area autografted (mean ± standard deviation)	8.4% ± 21.3	21.5% ± 34.8	0.0054
Deep partial-thickness second-degree and/or third-degree burns requiring excision/dermabrasion (surgical intervention)			
Number of wounds	163	170	
% of wounds requiring surgical intervention	24.5%	70.0%	<0.0001
% of wound wound area excised or dermabraded [1] (mean ± standard deviation)	13.1% ± 26.9	56.7% ± 43.3	<0.0001
Time to complete wound healing (time from FCE)**			
Number of patients[2]	70	78	
Days until the last wound healed (mean ± standard deviation)	36.2 ± 18.5	28.8 ± 15.6	0.0185
Time required for successful eschar removal			
Number of patients	67	73	
Days (mean ± standard deviation) from injury	2.2 ± 1.4	8.7 ± 5.7	<0.0001
Days (mean ± standard deviation) from consent	0.8 ± 0.8	6.7 ± 5.8	<0.0001
Patients for whom successful eschar removal was not reported	7	8	

[1] In cases of multiple surgical procedures, measured during the first procedure.

[2] All randomised patients for whom data on complete wound healing were available.

* This endpoint can only be assessed for second-degree wounds without third-degree burn areas, as the latter always require grafting.

** Informed consent form

Long-term results

A multicentre, non-interventional, blinded-observer study evaluated long-term scar formation and quality of life in adults and children who participated in the MW2004 study. The included population of 89 patients, including 72 adults and 17 paediatric patients (<18 years), was representative of the MW2004 study population.

Assessment of scarring at 2-5 years using the MVSS scale showed comparable results between the study arms, with a mean overall total score of 3.12 and 3.38 for this medicinal product and SOC, respectively (p=0.88).

QoL was assessed in adults using the SF-36 questionnaire. Mean scores for the various parameters were similar in both arms. The overall score for the physical component (51.1 and 51.3, respectively) and the overall score for the mental component (51.8 and 49.1, respectively) were comparable between the two arms.

Time to complete wound healing

In the DETECT study (MW2010), the median time to complete wound healing estimated by the Kaplan-Meyer method was 27 days for the NexoBrid arm and 28 days for the SOC arm. The p-value of 0.0003 confirmed the non-inferiority (non-inferiority margin of 7 days) of the NexoBrid treatment arm compared to SOC. The median time calculated with actual data was 23 days for both the NexoBrid and SOC arms. The combined healing data results from the two Phase 3 studies support the non-inferiority of NexoBrid compared to SOC with a non-inferiority margin of 7 days. Based on the combined data from the DETECT study and the MW2004 study, the time to complete wound healing was slightly longer in the NexoBrid arm than in the SOC arm when estimated using the Kaplan-Meyer method (median time 30.0 days vs. 25.0 days) or calculated using actual data (mean 31.7 days vs. 29.8 days). According to the non-inferiority analysis, the time to wound healing was less than 7 days longer with NexoBrid than with SOC (non-inferiority p=0.0006).

Paediatric study MW2012 (CIDS)

This was a randomised (1:1), open-label, SOC-controlled, parallel-group study conducted in 145 hospitalised patients (aged 0-18 years) with deep second-degree or third-degree thermal burns affecting 1% to 30% of the total body surface area (mean tw area: 5.57% of TBSA). Patients were randomised to receive this medicinal product (2 g of powder in 20 g of gel for 180 cm^2 for 4 hours) or SOC (surgical and/or non-surgical interventions to remove eschar). The study had three co-primary endpoints: median time to complete debridement, percentage of surgically excised wound area, and cosmesis and functional status of the skin 12 months after wound healing (Modified Vancouver Scar Scale score). Demographic data and key results are presented in the table below.

A total of 145 patients were randomised and included in the Full Analysis Set (FAS): 72 in the medicinal product arm and 73 in the SOC arm. Of these patients, 139 (95.9%) were treated and included in the Safety Analysis Set (SAS) population: 69 (95.8%) in the medicinal product arm and 70 (95.9%) in the SOC arm.

The age distribution was as follows (this medicinal product versus SOC): 0-11 months: 4 versus 4, 12-23 months: 19 versus 18, 24 months–3 years: 15 versus 15, 4-11 years: 25 versus 25, and 12-18 years: 9 versus 11.

Overall, patient age, ethnicity, height, weight and body mass index (BMI) were comparable across treatment arms. At the patient level, the mean %TBSA of TW was 5.85% for patients in the medicinal product arm versus 5.30% in the SOC arm.

Efficacy results:

Compared to SOC, treatment with the medicinal product significantly reduced the time required for complete eschar removal and the mean percentage of the wound area surgically excised for eschar removal. Patients treated with the medicinal product had fewer surgical excisions than patients receiving SOC (see table).

	NexoBrid (N=72)	**SOC (N=73)**	**p-value**
Age (mean, standard deviation)	5.71 (4.84)	5.83 (4.91)	
Outcomes			
Time to complete eschar removal			
Median, days (FAS)	0.99	5.99	0.0008
Percentage of wound area surgically excised (FAS)			
Mean ± standard deviation (FAS)	1.5 ± 12.1	48.1 ± 46.6	< 0.0001
MVSS score at 12 months			
Mean ± standard deviation (FAS)	3.83 ± 2.88	4.86 ± 3.26	< 0.0001 (Non-inferiority demonstrated)
Incidence of surgical excision (%)			
Proportion and number of patients requiring surgical excision for eschar removal (FAS)*	8.33	64.38	
Mean time to healing of the last wound – observational data (days)			
Mean ± standard deviation (FAS)	28.65 ± 16.56	27.74 ± 18.15	

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

The mean change in haemoglobin level after debridement, both at the patient level and at the intervention level, was lower in patients treated with the medicinal product compared to SOC.

Time to complete wound healing

The median time to complete wound healing (>95%) at the TW level, estimated using the Kaplan-Meier method, was comparable between SOP and treatment arms. In the pooled adult population, the median time to complete wound healing estimated by Kaplan-Meier analysis (clustered data from a patient's TW) was (this medicinal product [N = 280] versus SOC [N = 179]): 32 (95% CI: 29.0–34.0) days versus 28 (95% CI: 24.0–29.0) days, respectively. In the pooled paediatric population, the time to complete wound healing (> 95%) at the TW was comparable in the medicinal product arm and the SOC arm. The median time estimated according to the Kaplan-Meier analysis was (this medicinal product [N = 89] versus SOC [N = 86]): 31 (95% CI: 27.0–36.0) days versus 31 (95% CI: 24.0–37.0) days, respectively.

The results from both populations support the non-inferiority of this medicinal product compared to SOC, based on a non-inferiority margin of 7 days.

Long-term results (12 months)

With regard to cosmesis and functional status assessed at 12 months, measured by MVSS, the non-inferiority of treatment with the medinal product compared with SOC was demonstrated (p-value < 0.0001) with a non-inferiority margin of 1.9.

Pharmacokinetics

Adult population

Absorption

Pharmacokinetic analyses were performed in a subgroup of patients treated with NexoBrid who participated in the MW2008 study and the MW2010 (DETECT) study, using the same bioanalytical method.

After topical application of NexoBrid, systemic exposure was observed in all patients. In general, NexoBrid is rapidly absorbed with a median t_{max} of 4 hours (duration of treatment application). Exposure to NexoBrid is observed with quantifiable serum concentrations within 48 hours after dose administration.

The exposure results from the MW2008 and MW2010 studies are described below.

In each study, C_{max} and dose-normalised C_{max} after the first and second applications were comparable. Comparison of AUC_{0-4} and dose-normalised AUC_{0-4} normalised to dose for the first application compared to the second application indicates that exposure was slightly higher after the second application, but comparable (less than 2-fold). Not all patients had values beyond 4 hours; therefore, AUC_{last} values cover only 4 hours of exposure for some patients and 48 hours for others.

In both studies, serum C_{max} and AUC_{0-4} were statistically significantly correlated with dose or %TBSA, suggesting an increase in exposure dependent on dose- or treatment area. The depth of the wound treated with NexoBrid has a negligible impact on systemic exposure.

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

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

* Data are presented as mean ± standard deviation, except for t_{max} which is presented as median (Min-Max)

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

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

Distribution

According to the literature, approximately 50% of bromelain binds in human plasma to antiproteases, α_2-macroglobulin and α_1-antichymotrypsin.

Metabolism

No data available

Elimination

The median terminal elimination half-life was 12 ± 4.4 hours in study MW2008-09-03. No quantifiable concentrations were detected in the majority of patients when assessed after 72 hours.

Kinetics in specific patient groups

Children and adolescents

Exploratory pharmacokinetic analyses were performed in a PK sub-study of the MW2012 (CIDS) study. These analyses focused on serum drug concentration data over time.

Blood samples for PK analysis were collected from 16 patients treated with the medicinal product. All patients received a single application.

Signs of systemic serum exposure were observed in all 16 patients for whom PK samples were available. Concentrations increased fairly rapidly, with median T_{max} values ranging from 2 to 4 hours, which corresponds to the period of topical administration.

Systemic exposure to the medicinal product was in correlation with the topical dose applied.

The exposure results are presented in the table below.

Summary of PK parameters measured in patients in the MW2012 study

(Age group, years)	N	T_{max} Median (range) (h)	C_{max} (ng/mL)	C_{max} /Dose /ng/mL/g)	AUC_{0-4} (h*ng/mL)	AUC_{0-4} / Dose (h*ng/mL)	AUC_{last} (h*ng/mL)	AUC_{last} Dose (h*ng/mL/g)
< 2	2	2.00	200	66.7	476	159	876	292
4-11	5	4.0 (2.0-4.0)	205 ± 169	32.8 ± 23.9	416 ± 259	67.9 ± 44.7	2240 ± 2220	366 ± 350
12–18	5	4.0 (2.0-4.0)	180 ± 114	19.2 ± 7.50	499 ± 315	53.3 ± 20.4	1560 ± 887	174 ± 67.4

*Ten patients were included in the main PK analyses.

Elimination

No quantifiable concentrations of the drug were found in the majority of patients after 48 hours, and no quantifiable concentrations were detected in any patients at 72 hours.

Preclinical data

Repeat dose toxicity

A single intravenous infusion of a solution prepared from NexoBrid powder was well tolerated in minipigs at dose levels up to 12 mg/kg (achieving plasma levels 2.5 times higher than those achieved in humans after application of the recommended clinical dose to 15% of the total body surface area, TBSA), but higher doses were highly toxic, causing haemorrhage in several tissues. Repeated intravenous injections of doses up to 12 mg/kg every three days in minipigs were well tolerated for the first four injections, but severe clinical signs of toxicity (e.g. haemorrhages in several organs) were observed following the next two injections. These effects could still be observed after a 2-week recovery period.

Mutagenicity

NexoBrid was not genotoxic in standard *in vitro* tests (reverse mutation test in bacteria [Salmonella thyphimurium], *in vitro* mammalian chromosome aberration test in Chinese hamster V79 cells) or *in* vivo tests (micronucleus test in mouse bone marrow cells).

Carcinogenicity

No carcinogenicity studies have been conducted with NexoBrid.

Developmental toxicity

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

Toxicity analysis in juvenile animals

The toxicological results of the drug in juvenile mini-pigs were comparable to those in adults. Topical application of the drug (0.09 g/g) to young pigs (aged 2 months) did not result in any notable local or systemic toxicological effects after application to burns in a formulation and dosage regimen relevant to human use of the product. After repeated intravenous injections of doses of 4, 8 and 12 mg/kg every three days to juvenile mini-pigs, related changes were observed after the fifth dose on day 10 in all dose groups. Observations included convulsions and skin redness, as well as decreased activity, breathing difficulties and ataxia in some animals.

A trend towards increased QT and QTc intervals was observed on day 10 after dosing in treated animals. These values were obtained after significant clinical observations, which are described above.

Local toxicity

This medicine did not cause significant irritation when applied to intact minipig skin, but caused severe irritation and pain when applied to damaged (abraded) skin.

Other information

Incompatibilities

Topical medicines (such as silver sulfadiazine or polyvidone iodine) applied to the wound site must be removed and the wound cleaned before applying NexoBrid. Any remaining antibacterial medicine s could alter the activity of NexoBrid, reducing its effectiveness.
This medicine must not be mixed with other medicines.

Shelf life

The medicine must not be used after the date shown on the container after "EXP".
From a microbiological point of view and as the enzymatic activity of the product gradually decreases after mixing, the reconstituted product should be used immediately after preparation (within 15 minutes).

Special precautions for storage

Store and transport refrigerated (between 2°C and 8°C).
Store upright to keep the gel at the bottom of the vial, in the original outer packaging, protected from light.
Do not freeze.
Keep out of the reach of children.

Instructions for handling

Occupational exposures to bromelain leading to sensitisation have been reported. Sensitisation may have occurred through inhalation of bromelain powder. Allergic reactions to bromelain include anaphylactic reactions and other immediate reactions with manifestations such as bronchospasm, angioedema, urticaria, and mucosal and gastrointestinal reactions. When mixing the powder of this medicine with the gel, appropriate handling, including wearing gloves and protective clothing as well as protective eyewear and a surgical mask, is required (see also section "Warnings and precautions"). The powder must not be inhaled.
Accidental exposure to the eyes must be avoided. In case of eye exposure, the exposed eyes must be rinsed with plenty of water for at least 15 minutes. In case of skin exposure, NexoBrid must be rinsed off with water.

<u>Preparation of NexoBrid gel (mixing the powder with the gel)</u>

- NexoBrid powder and gel are sterile. Aseptic technique must be used when mixing the powder and gel.

- The powder vial should be opened by carefully removing the aluminium seal and removing the rubber stopper. The powder should not be inhaled. Appropriate precautions should be taken when handling the debriding agent (including wearing gloves, a protective gown and a protective mask).
- When opening the gel bottle, check that the tamper-evident ring separates cleanly from the bottle cap. If the tamper-evident ring was already detached from the cap before opening, the gel bottle must be discarded and a new gel bottle must be used.
- The powder is then poured into the gel bottle.
- The powder and gel must be mixed thoroughly until a uniform, slightly off-white to slightly brown mixture is obtained. The powder and gel should generally be mixed for 1 to 2 minutes.
- The gel must be prepared at the patient's bedside.

Any unused medicine or waste must be disposed of in accordance with current regulations.

Authorisation number

68012 (Swissmedic)

Packs

Each package contains 1 vial of powder and 1 vial of gel.
NexoBrid 5 g [A]

Marketing authorisation holder

Triskel Integrated Services, Le Grand-Saconnex-Genève

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