THE EDUCATIONAL MATERIAL IS MANDATORY AS A CONDITION OF THE MARKETING AUTHORISATION IN ORDER TO FURTHER MINIMISE IMPORTANT SELECTED RISKS

EDUCATIONAL MATERIALS

The main purpose of this educational material is to inform medical personnel at burn centres about:

1. NexoBrid instructions for use.
2. Required risk-minimising activities shown to be effective in reducing important safety risks of pain, pyrexia and wound infection, which were identified and managed through corrective actions during the NexoBrid clinical development programme.
3. Required risk-minimising activities for potential risks of increased tendency to bleeding, severe irritation, allergic reaction, increase mortality in patients with cardiopulmonary disease and off-label use.
4. Monitoring activities post NexoBrid application.

INTRODUCTION:

Burns are among the most severe traumas in the modern, developed parts of the world, and even more so in less developed areas.

The burn eschar may be of different thickness and appearance corresponding to the cause, depth and extent of the trauma. It may include part of or the entire thickness of the skin and even deeper tissues.

Dead eschar serves as a medium for bacterial growth, and is therefore a source of infection, contamination and sepsis, which may ultimately lead to the patient's death. The presence of the eschar promotes extension of the damage into the neighbouring, healthy tissues and prevents accurate diagnosis. Very often the extent and depth of tissue damage may only be determined a few days after injury when the damage has extended into the surrounding tissues.

Some studies highlight the relation between the presence of the eschar and deterioration of the general immune response, a phenomenon that promotes sepsis.

Circumferential burns especially of the extremities may cause interstitial and compartment elevated pressure (Burn Induced Compartment Pressure: BICS) with permanent damage to soft tissues, nerves and muscles.

The eschar prevents the initiation of the wound healing process (epithelialization). This delay causes granulation tissue formation that later will evolve into heavy and deforming scar (healing by secondary intention).

Early as possible eschar removal (debridement) of the offending eschar to prevent eschar-related complications is the cornerstone of the modern treatment of burns.

NEXOBRID® GENERAL BACKGROUND

Product description:

A novel, enzymatic eschar removal medicinal product for topical application.

Lyophilised sterile mixture of proteolytic enzymes (concentrate of proteolytic enzymes enriched in bromelain) from pineapple plant stem.

Product presentation:

Vial of sterile lyophilized powder (2g or 5g)

Bottle of sterile gel vehicle (20g or 50g)

Product indication:

Removal of eschar in adults with deep partial- and full-thickness thermal burns.

INSTRUCTIONS FOR USE - STEP BY STEP TREATMENT GUIDE:

BEFORE PRESCRIBING NEXOBRID:

Healthcare professional and treating physician (burn specialist) should be aware of the following before prescribing NexoBrid.

- NexoBrid should only be applied by trained healthcare professionals in specialist burn centres.
- The Total Body Surface Area (TBSA) of the treated burn should be limited to 15% TBSA due to limited pharmacokinetic data in patients with TBSA of more than 15% and due to records of coagulopathy events that were observed in animals' studies. NexoBrid should not be applied to more than 15%Total Body Surface Area (TBSA).
- The use of NexoBrid is contraindicated in patients allergic to the active substance concentrate of proteolytic enzymes enriched in bromelain, to pineapples or papain, or to any of the excipients.

- Healthcare professionals need to be aware of the potential risk of allergic reaction in subsequent use of NexoBrid in burn injuries and patients that are re-exposed to bromelain-containing products at a later point in time.
- Healthcare professionals need to be aware of the risk of increased mortality in patients with cardiopulmonary diseases. Therefore NexoBrid should be used with caution in patients with cardiopulmonary and pulmonary disease, including pulmonary burn trauma and suspected pulmonary burn trauma.

PRE DEBRIDEMENT

The treating physician needs to be aware of the following prior to applying NexoBrid

- NexoBrid treatment is associated with pain. Therefore the treating physician has to implement adequate pain management and has to administer preventive analgesia/sedation medication to the patient before applying NexoBrid
- The treating physician has to apply a dressing soaked with an antibacterial solution to the cleaned burns and leave it in place for at least 2 hours in order to minimise potential for wound infection and pyrexia
- In order to prevent possible irritation of surrounding skin by inadvertent contact with NexoBrid, the treating physician has to apply a layer of a sterile fatty ointment for protection of these areas.

The treating physician should follow the wound cleansing process (section 1) and wound preparations pre-debridement procedure (section 2) described below.

1. Wound Cleansing

Prior to debridement, the initial care of the burn wound starts with standard cleaning that removes all gross contaminants, soot and blisters. The following wound cleansing procedure is designed also to protect the wound by preventing desiccation and contamination by microorganisms.

a. Preventive analgesia/sedation medication must be administered to the patient along the lines of routinely and commonly practiced treatment for pain management during an extensive burn dressing change and wound cleansing. It is used to ensure pain-free wound care so that the entire treatment course (with NexoBrid) is performed in a comfortable manner for the patient.

b. Remove dressings and discontinue topically applied medication at the wound site. Topical medication (such as silver or iodine compounds) may interfere with NexoBrid® activity

c. Cleanse the wound thoroughly with saline, soap or antibacterial solution, at the discretion of the physician. Blisters (superficial keratin layer) should be removed by

common procedures such as rubbing with sterile gauze, saline soaking, cleansing sponge etc.

d. Apply a dressing soaked with an antibacterial solution (e.g. Hypertonic saline solution, 3-5% Sulfamylon or 0.05-0.5% Chlorhexidine) to the cleaned burns and leave in place for at least 2 hours. This dressing is composed of multiple layers of sterile absorbing gauze or a similar non-woven absorbing material. The sterile gauze is saturated with the antibacterial solution and is applied to be in direct contact with the entire burned area. The dressing is then covered with a fluffy bandage, such as a K-bandage, to hold the sterile gauze in place. The sterile gauze dressing should remain wet until it is removed prior to the initiation of the debridement procedure in order to prevent desiccation and gross contamination of the burn. The soaking-dressing must be changed at least every 12 hours if NexoBrid treatment is not performed immediately.

e. After the wound is soaked for at least two hours, remove the fluffy bandage and the sterile gauze dressing. The wound is reassessed to ensure that the superficial keratin layer (blisters) has been removed. For deep, charred, flame burns, keratin removal may be difficult. Thorough scraping with gauze or cleansing sponge may be needed to remove the keratin layer in such cases.

2. Wound Preparation

2.1. Preparation for NexoBrid Application

a. Use pain management as commonly practiced for an extensive dressing change; it should be initiated at least 15 minutes prior to NexoBrid application as described in Section 1a.

b. Clean the wound thoroughly and remove all of the superficial keratin layer or blisters from the wound area, as the keratin will isolate the eschar from direct contact with NexoBrid and prevent eschar removal by NexoBrid.

c. Remove all topically applied antibacterial medicinal products before applying NexoBrid. Remaining antibacterial medicinal products may interfere with the activity of NexoBrid by decreasing its efficacy.

d. Surround the area from which you wish to remove the eschar with a sterile paraffin ointment adhesive barrier by applying it a few centimetres outside of the treatment area see Figure 1. 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.

e. Protect areas of abraded skin from possible irritation by inadvertent contact with NexoBrid, by applying a layer of a sterile fatty ointment.

f. Sprinkle the burn wound with sterile isotonic sodium chloride 9 mg/ml (0.9%) solution. The wound must be kept moist during the application procedure Figure 2.

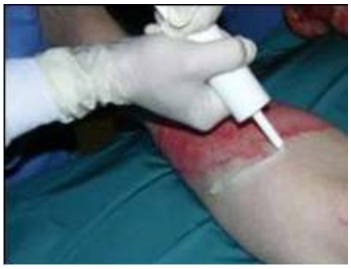

Figure 1: Application of Adhesive Barrier around the Treatment Area

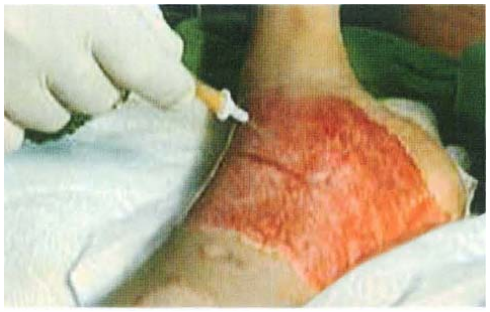

Figure 2: Application of Sterile Isotonic Sodium Chloride Solution

2.2. NexoBrid Preparation

a. Assess the patient's target wound area to determine the amount of NexoBrid to be used during treatment.

b. NexoBrid powder and gel are supplied in two different quantities: 2g NexoBrid powder plus 20g gel to cover 100 cm^2 or 5g NexoBrid powder plus 50g gel to cover 250 cm^2 of burn wound.

c. Mix 2g or 5g of NexoBrid sterile powder as needed, 20g or 50g of sterile Gel (ratio of 1:10). The NexoBrid powder and gel are mixed using a sterile tongue depressor at the patient's bedside until a homogenous, light brown mixture is achieved (see Figure 3).

Figure 3: NexoBrid Powder and Gel Homogenous Mixture

3. NexoBrid Treatment (Debridement)

Due to potential risk of pain, wound infection and increased tendency for bleeding, patients should be monitored for the following during NexoBrid treatment:

- 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

NexoBrid should not be applied to more than 15% Total Body Surface Area (TBSA).

Step by step description of the debridement phase of the treatment:

a. Apply NexoBrid topically to the moistened burn wound within 15 minutes of mixing,, at a thickness of 1.5 to 3 millimetres (Figure 4). The NexoBrid gel is applied so that it covers the entire wound area, filling the entire area confined by the sterile paraffin ointment adhesive barrier (Figure 5).

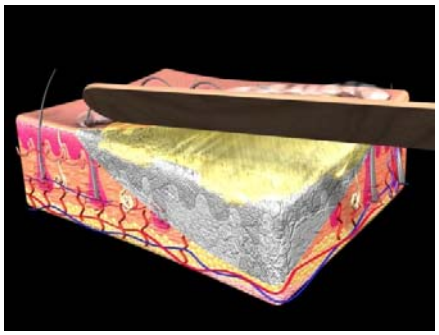

Figure 4: Application of NexoBrid to Treatment Area

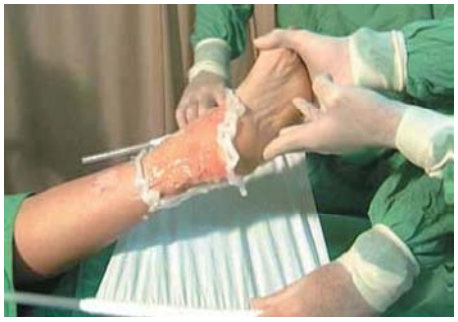

Figure 5: NexoBrid Coverage

b. Cover the wound (Figure 6) with a sterile occlusive film dressing that adheres to the applied sterile adhesive barrier material applied (Figure 7). 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.

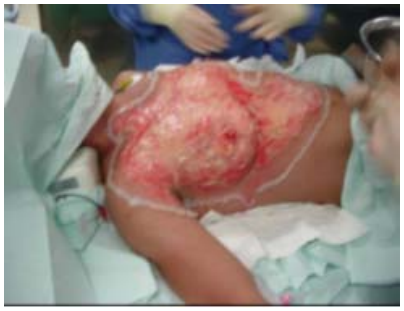

Figure 6: Treatment Area

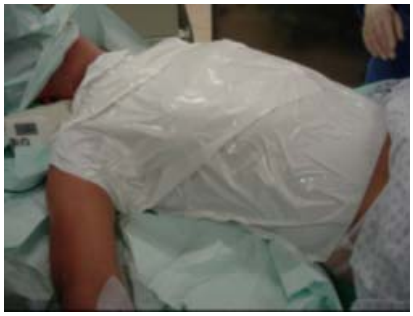

Figure 7: Application of Sterile Occlusive Film Dressing

c. Cover the dressed wound with a loose, thick fluffy dressing, held in place with a bandage (Figure 8).

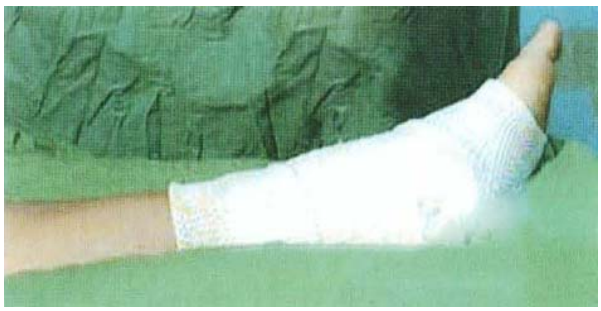

Figure 8: External, Stabilizing Dressing

d. Keep the dressing in place for 4 hours.

e. Discard all unused NexoBrid gel.

4. Post Debridement

4.1. Removal of NexoBrid dressing

a. Administer appropriate preventive analgesia medicinal products (see Section 1.a).

b. After 4 hours of NexoBrid treatment, remove the occlusive film dressing using aseptic techniques.

c. Remove the adhesive barrier using a sterile blunt-edged instrument (e.g., tongue depressor).

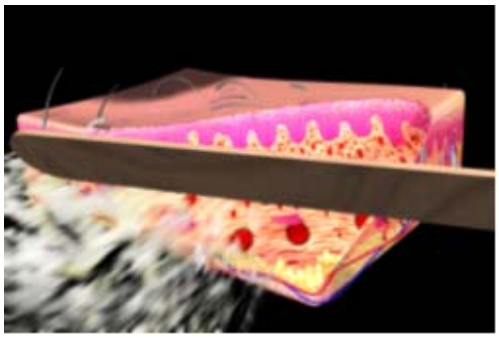

Figure 9: Removal of Dissolved Eschar

d. The dissolved eschar must be removed from the wound. Wipe it away with a sterile blunt-edged instrument as shown in Figure 9.

e. Wipe the wound 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. Rub the treated area 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.

f. Apply a dressing soaked with an antibacterial solution (e.g. 3-5% sulfamylon or 0.05-0.5% chlorhexidine) to the treatment area for an additional 2 hours.

4.2. Wound Assessment

After soaking the wound with antibacterial solution for 2 hours (see 4.1.f), remove the antibacterial solution and assess the wound for the following, as presented in

Figure 10.

- Completeness of Debridement
- % TBSA and burn depth in order to determine further wound management.

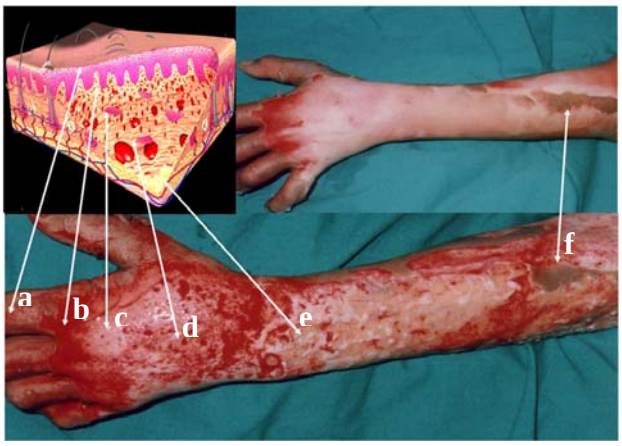

Figure 10: Wound Bed Assessment

a. Non burned skin, uninjured by NexoBrid
b. Superficial dermal burn with bleeding
c. Mid depth dermal burn with well preserved dermal collagen matrix
d. Deep dermal burn with larger and wider spaced bleeding capillaries and a very thin dermal matrix
e. Full Thickness burn
f. Non dissolved eschar protected by blister that was not removed prior to NexoBrid application

5. Repeat Debridement

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

6. Wound Care After Debridement

- Cover the debrided area immediately post debridement 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, use a soaking wet-to-dry dressing to remove remaining dissolved eschar.
- Clean and refresh the debrided bed before application of the grafts or primary dressing, by, e.g., brushing or scraping to promote dressing adherence.

Wounds with areas of full-thickness and deep burns 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. Cover the debrided wound bed promptly after debridement and keep moist until the grafting is done, with temporary dressings (soaking, Allografts or Xenografts, perforated

biological dressing films, etc) to prevent desiccation. Use of fatty ointment to prevent desiccation is not recommended prior to autografting.

Just prior to autografting, while the patient is under general anesthesia for the autograft harvesting, remove the temporary dressings, then wipe and scrape the raw surface of the debrided bed to remove fibrin deposits and open the occluded blood vessels as preparation for the engraftment.

As with any autografting procedure the graft should be applied on a clean and viable bed, stabilized to prevent movement and shearing and dressed with first layer of paraffin gauze covered with thick layer of absorbent compressing dressings. Negative pressure dressing may be applied over the graft for few days to promote graft take. The post graft care follows standard of care and is combined with scar modulation (Silicon surface and pressure garments).

Debrided dermal bed can be treated toward epithelialization over dermis by using dressing that will keep the bed moist, preventing desiccation and tissue death, and provide the conditions for epithelialization. Granulation tissue should be controlled, by short (2-3 days) courses of corticosteroid ointment, or if epithelialization and wound closure do not progress by autorafting of the not healed areas.

In NexoBrid studies wounds with visible and rich dermal remnants were allowed to heal by spontaneous epithelialization under proper dressing. In several cases healing was delayed and autografting was required at a later stage, leading to delays in wound closure. Delayed wound closure may be associated with increased risk of wound-related complications (e.g. graft failure, infection). Therefore, wounds with areas of full-thickness and deep burn without reasonable likelihood of spontaneous epithelialization 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

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

The need for blood transfusion has been observed in both NexoBrid and SOC treated patients; across treatment arms. 91.2% of blood transfusions in study MW2004-11-02 were in proximity to and clearly associated with surgical procedures that are recognized in the literature to be directly associated with blood loss [1,2].

Late excisional surgery may possibly be associated with greater blood loss [3,4] and this should be taken into consideration by the physicians in the choice of wound closure strategy for NexoBrid-debrided wounds.

7. Risk Minimising Activities for Identified and Potential Risks

The treating physician should be aware of the following risks (prior, during and after NexoBrid treatment) listed below. The corresponding measures aiming to mitigate and minimize these risks are listed below

Important identified Risks	**Required Risk Minimisation Activity with use of NexoBrid**
Pain	Use of preventive pain management as commonly practiced during extensive routine burn dressing changes in current standard of care. The pain management should be initiated at least 15 minutes prior to NexoBrid application. An example of analgesia/sedation is the appropriate combination of fentanyl, midazolam and ketamine or morphine and similar analgesia protocols as commonly practiced at burn centres that can be given by bolus and dripping intravenous administration. Epidural anaesthesia or analgesia can be used in the care of the lower body areas at the discretion of the ohysician. ***Caution:*** *Pain-relieving topical medicaments (such as gels, creams, ointments, liquids etc.) on burns may be applied on very limited areas but care should be taken in using them since their systemic absorption through extensive burns surface may be dangerous as well as may cause hypersensitivity to these local anaesthetics.*
Pyrexia	Apply antibacterial soaking (e.g., hypertonic saline solution, 3-5% sulfamylon or 0.05-0.5% chlorhexidine) for 2 hours before and after NexoBrid treatment to reduce pyrexia.
Wound infection	• Apply standard topical care techniques to prevent bacterial contamination and infiltration of the wound like anti-bacterial/anti-microbial soaking. • Refrain from using NexoBrid on highly contaminated eschar. • Wound cleansing and soaking prior to use of NexoBrid is required to protect the wound by preventing desiccation and contamination by microorganisms; the initial care of the burn wound begins with a general and routine cleaning that removes all gross contaminants, sooth and blisters. • A dressing soaked with an antibacterial solution (e.g., Hypertonic saline solution, 3-5% Sulfamylon or 0.05-0.5% Chlorhexidine) is to be applied to the wound and left in place for at least 2 hours. The dressing is then covered with a fluffy bandage, such as a K-bandage, to hold the sterile gauze in place. The sterile gauze dressing should remain wet until it is removed prior to the initiation of the debridement procedure to prevent desiccation and gross contamination of the wound. • After the wound is soaked for at least two hours, the fluffy bandage and the sterile gauze dressing is to be removed. The wound is reassessed to ensure that the superficial keratin layer (blisters) has been removed. For deep, charred, flame burns, keratin removal may be difficult. A thorough scraping with gauze or cleansing sponge

Important identified Risks	Required Risk Minimisation Activity with use of NexoBrid
	may be needed to remove the keratin layer in this instance. • The soaking-dressing must be changed at least every 12 hours.
Delay in time to complete wound closure	• 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

Important potential Risks	Required Risk Minimisation Activity with use of NexoBrid
Increase tendency to bleeding	• Reduction of platelet aggregation and a moderate increase in partial thromboplastin time has been reported as a possible effect following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. • Patients should be monitored for possible signs of coagulation abnormalities. Should a clinically relevant effect have been observed, confirm that it has subsided before any subsequent NexoBrid application. • 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. • Caution and monitoring is needed when prescribing concomitant medicinal products that affect coagulation.
Severe Irritation	To prevent possible irritation of abraded skin by inadvertent contact with NexoBrid, such areas (adjacent to burn area) can be protected by a layer of a sterile fatty ointment (e.g. Adhesive Barrier).
Increased mortality in patients with Cardiopulmonary disease	NexoBrid should be used in caution in patients with cardiopulmonary and chronic or acute pulmonary disease or injury (i.e. smoke inhalation injury).
Allergic reaction	• Use of NexoBrid is contraindicated if hypersensitivity to bromelain, pineapples or any of the excipients of NexoBrid powder or Gel Vehicle is suspected*. • In case of skin exposure, NexoBrid should be rinsed off with water to reduce the likelihood of skin sensitisation. • 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. • 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 signs of local and systemic allergic reactions.

Important potential Risks	Required Risk Minimisation Activity with use of NexoBrid
	• 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. In NexoBrid, the powder containing enriched bromelain proteolytic enzymes is present in the form of a sterile lyophilised cake, reducing the likelihood of inhalational exposure. Avoid accidental eye exposure. In case of eye exposure, irrigate exposed eyes with copious amounts of water for at least 15 minutes. In case of skin exposure, rinse NexoBrid off with water.
Off label use in facial burns, perineum or genital area, single application of Nexobrid to wounds >15% TBSA in one session, use in repeated applications	Appropriate statements were included in the product SmPC: • Section 4.2 (Posology and method of administration): "NexoBrid should not be applied to more than 15% Total Body Surface Area (TBSA) … A total wound area of not more than 15% TBSA can be treated with NexoBrid. A second and subsequent application is not recommended". • Section 4.4 Special warnings and precautions: Burns for which there is limited or no experience: There is no experience on the use of NexoBrid in perineal and genital burns. There is limited information on the use of NexoBrid in facial burn wounds".

* Cross sensitivity between bromelain and papain as well as latex proteins, bee venom, and olive tree pollen has been reported in the literature.

PATIENT MONITORING POST NEXOBRID ADMINISTRATION

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), monitor patients treated with NexoBrid for the following:

- 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).

Treatment or prophylactic measures (e.g., insertion of a nasogastric tube) should be initiated as indicated.

References

1 Mzezewa, S., et al., A prospective double blind randomized study comparing the need for blood transfusion with terlipressin or a placebo during early excision and grafting of burns. Burns, 2004. 30(3): p. 236-40

2 Luo, G., et al., Blood loss during extensive escharectomy and auto-microskin grafting in adult male major burn patients. Burns, 2011. 37(5): p. 790-93

3. Kagan R., et al., American burn association white paper. Surgical Management of the Burn Wound and Use of Skin Substitutes. American burn association, 2009

4 Desai, M.H., et al., Early burn wound excision significantly reduces blood loss. Ann Surg, 1990. 211(6): p. 753-9; discussion 759-62