רופא/ה ,רוקח/ת נכבד/ה,

הנדון: NexoBrid 2g and NexoBrid 5g gel and powder for gel

חברת מדיוונד ישראל בע"מ מבקשת להודיעכם כי העלונים לרופא של התכשיר שבנדון התעדכנו במאי 2022.
פרטי העדכונים העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום עם קו תחתון, טקסט שהושמט מסומן כטקסט ~~כחול עם קו חוצה~~, טקסט המהווה החמרה מודגש בצהוב) , אך קיימים עדכונים נוספים.

ההתוויות להן רשום התכשיר:
NexoBrid is indicated for removal of eschar in adults with deep partial and full thickness thermal burns.

צורת מינון:

Powder and gel for gel.

מרכיב פעיל:

Concentrate of proteolytic enzymes enriched in bromelain

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות.
כמו כן, מצורפים לפרסום זה וניתן לקבל העתק מודפס באמצעות פנייה לבעל הרישום:
מדיוונד בע"מ, רחוב הירקון 42, יבנה, טל' 077-9714100.

בברכה,
פאני מגריש
רוקחת ממונה
מדיוונד בע"מ

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 1 % Total Body Surface Area (TBSA) of an adult, with a gel layer thickness of 1.5 to 3 mm~~100 cm^2~~.
5 g NexoBrid powder in 50 g gel is applied to a burn wound area of 2.5 % Total Body Surface Area (TBSA) of an adult, with a gel layer thickness of 1.5 to 3 mm~~250 cm^2~~.

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).

- Enzymatic debridement is a painful procedure and requires adequate analgesia and/or ~~anesthesia~~anaesthesia. Pain management must be used as commonly practiced for an extensive dressing change; it should be initiated at least 15 minutes prior to NexoBrid application.

- The wound must be cleaned thoroughly and the superficial keratin layer or blisters removed from the wound area, as the keratin will isolate the eschar from direct contact with NexoBrid and prevent eschar removal by NexoBrid.
- Dressing soaked with an antibacterial solution must be applied for 2 hours.
- All topically applied antibacterial medicinal products must be removed before applying NexoBrid. Remaining antibacterial medicinal products may reduce ~~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

- Moisten the area to be treated by sprinkling sterile saline onto the area bordered by the fatty ointment adhesive barrier.
- Within 15 minutes of mixing, NexoBrid must be applied topically to the 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

- Removal of NexoBrid is a painful procedure and requires adequate analgesia and/or anaesthesia. Appropriate preventive analgesia medicinal products must be administered at least 15 minutes prior to NexoBrid application.
- After 4 hours of NexoBrid treatment, the occlusive dressing must be removed using aseptic techniques.
- The adhesive barrier must be removed using a sterile blunt-edged instrument (e.g., tongue depressor).
- The dissolved eschar must be removed from the wound by wiping it away with a sterile blunt-edged instrument.
- The wound must be wiped thoroughly first with a large sterile dry gauze or napkin, followed by a sterile gauze or napkin that has been soaked with sterile isotonic sodium chloride 9 mg/ml (0.9%) solution. The treated area must be rubbed until the appearance

- of a pinkish surface with bleeding points or a whitish tissue. Rubbing will not remove adhering undissolved eschar in areas where the eschar still remains.
- A dressing soaked with an antibacterial solution must be applied for an additional 2 hours.

4.4 Special warnings and precautions for use

Hypersensitivity reactions, skin exposure

The potential of NexoBrid (a protein product) to cause sensitisation should be taken into account.
There have been reports of serious allergic reactions including anaphylaxis (with manifestations such as rash, erythema, hypotension, tachycardia) in patients undergoing debridement with NexoBrid. In these cases, a causal relationship to NexoBrid was considered possible, but possible allergy to concomitant medications such as opioid analgesics should also be considered.
Allergic reactions to inhaled bromelain have been reported in the literature (including anaphylactic reactions and other immediate-type reactions with manifestations such as bronchospasm, angiooedema, urticaria, and mucosal and gastrointestinal reactions). No occupational hazard was found in a study assessing the amount of airborne particles during NexoBrid Gel preparation.
In addition, a delayed-type allergic skin reaction (cheilitis) after longer-term dermal exposure (mouthwash) as well as suspected sensitisation following oral exposure and following repeated occupational airway exposure have been reported.
History of allergy needs to be established prior to the administration (see sections 4.3 and 6.6).

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.

Enzymatic debridement is a painful procedure, and may only be administered after adequate analgesia and/or anesthesia has been established.

Burn wounds for which NexoBrid is not recommended

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.
- foot burns in diabetic patients and patients with occlusive vascular disease

- in electrical burns.

Burns for which there is limited or no experience

There is no experience of the use of NexoBrid on:
- perineal and genital burns.

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 (see section 4.2).

There are literature reports of successful~~is limited information on the~~ use of NexoBrid on facial burn wounds. Burn surgeons without experience in using NexoBrid should not start using it on facial burn wounds. NexoBrid must be used with caution in such patients.

Eye protection

Direct contact with the eyes must be avoided. Eyes must be carefully protected during treatment of facial burns using fatty ophthalmic ointment on the eyes and adhesive barrier petroleum ointment around to insulate and cover the eyes with occlusive film.
In case of eye exposure, irrigate exposed eyes with copious amounts of water for at least 15 minutes. An ophthalmological exam is recommended prior to and after debridement.

Concentrate of proteolytic enzymes enriched in bromelain is systemically absorbed from burn wound areas (see section 5.2).
There is limited pharmacokinetic data in patients with TBSA of more than 15%. Due to safety considerations (see also section 4.4, Coagulopathy) 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 may be~~is~~ associated with increased risk of wound-related complications. Therefore, wounds with areas of full-thickness and deep burn that will not heal spontaneously by epithelialization in timely manner 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.

Coagulopathy

A~~It is not known if NexoBrid application has any clinically relevant effect on haemostasis. An increase in heart rate (including tachycardia), reduction~~ 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 not be used in patients with uncontrolled disorders of coagulation. NexoBrid ~~and~~ should be used with caution in patients under anticoagulant therapy or other drugs affecting coagulation, and ~~in patients with disorders of coagulation,~~in patients with low platelet counts and increased risk of bleeding from other causes e.g. peptic ulcers and sepsis. Patients should be monitored for possible signs of coagulation abnormalities and signs of bleeding.

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 reduce~~may interfere with~~ the activity of NexoBrid by decreasing its efficacy.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions of the use of NexoBrid are transient pyrexia/hyperthermia (incidence of 15.2% in 223 patients treated with NexoBrid in pooled studies MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02) and pain (incidence of 4.0% in 223 patients treated with NexoBrid in pooled studies MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02). The Adverse Reactions are detailed below. ~~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).~~

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*

Cardiac disorders
Common: Tachycardia*

Immune system disorders
Common: Non serious allergic reactions such as rash[a]
Not known: Serious allergic reactions including anaphylaxis [a]
a see section 4.4.

Description of selected adverse reactions

Pyrexia/hyperthermia
In pooled studies MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02 with routine antibacterial soaking of the treatment area before and after NexoBrid application (see section 4.2) pyrexia or hyperthermia was reported in 15.2% of patients treated with NexoBrid and in 11.3% of the control patients treated according standard of care (SOC).
In early studies without antibacterial soaking (Studies MW2001-10-03 and MW2002-04-01), pyrexia or hyperthermia was reported in 35.1% of NexoBrid-treated patients compared with 8.6% treated with SOC.

~~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 pooled studies MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02 where the NexoBrid regimen included recommended preventive analgesia as routinely practiced for extensive dressing changes in burn patients (see section 4.2) pain was reported

in 4.0% of patients treated with NexoBrid, and in 3.8% of the control patients treated according to SOC.
In early studies where analgesia was provided in NexoBrid-treated patients on an on-demand basis, pain was reported in 23.4% of patients treated with NexoBrid and in 5.7% in the SOC group.

~~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 infection
In pooled studies with routine antibacterial soaking of the treatment area before and after NexoBrid application (studies MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02 studies), the incidence of wound infection was 5.4% in the NexoBrid group and 8.1% in the standard of care group.

Wound complications
Wound complications reported include the following: wound deepening, wound desiccation, wound re-opening, graft loss/ graft failure, and local intradermal haematoma.
In pooled phase 2 and 3 studies (MW2001-10-03, MW2002-04-01, MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02) including 300 patients treated with NexoBrid and 195 patients treated with Standard of Care (SOC), the following incidence was reported: wound complication 3% in the NexoBrid treated patients and 1.5% in patients treated with Standard of Care (SOC), skin graft loss/graft failure 3% in the patients treated with NexoBrid and in 2.5% in patients treated with Standard of Care, wound decomposition 1% in both the NexoBrid and SOC treated patients, local intradermal hematoma 0.7% in NexoBrid treated patients and none in the SOC treated patients.

~~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'~~

רחוב הירקון 42 אזור תעשייה צפוני יבנה 8122745 | טל: 972-77-9714100+ | פקס: 972-77-9714111+
42 Hayarkon St. Industrial Zone Yavne 8122745 | Tel: +972-77-9714100 | Fax: +972-77-9714111
E-mail: mediwound@mediwound.com website: www.mediwound.com

~~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).~~

Tachycardia
In pooled phase 2 and 3 studies (MW2001-10-03, MW2002-04-01, MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02) 2.7% of patients experienced tachycardia in temporal proximity to NexoBrid treatment. Alternative causes of tachycardia (e.g. the general burn condition, procedures causing pain, fever and dehydration) should be considered.

~~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. NexoBrid is not indicated for use in patients younger than 18 years (see section 4.2).

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~~ When mixing NexoBrid powder with the gel, appropriate handling, including wearing of gloves and protective clothing as well as eye shielding glasses and a surgical mask, is required. The powder should not be inhaled. See also section 4.4.