▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – NEXOBRID® (ANACAULASE-BCDB)

1 NAME OF THE MEDICINE

NEXOBRID anacaulase-bcdb 4.85 g powder vial with diluent gel bottle composite pack

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 5 g lyophilized powder (containing 4.85 grams of anacaulase-bcdb) and one bottle of 50 g gel vehicle per composite pack.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder vial with diluent gel bottle composite pack.

The powder is off-white to light tan. The gel is clear and colourless.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NEXOBRID is indicated for eschar removal in adults and paediatric patients with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.

For further information on acceptable burn types, see Section 4.4 Special Warnings and Precautions.

4.2 DOSE AND METHOD OF ADMINISTRATION

NEXOBRID is only to be administered by a healthcare provider that has been trained to use the product. Healthcare providers should take precautions to avoid exposure to NEXOBRID during preparation and handling (e.g., use of gloves, surgical masks, as well as eye shielding glasses, other protective coverings, as needed).

NEXOBRID lyophilized powder and gel vehicle must be mixed prior to administration. Each vial of lyophilized powder, bottle of gel vehicle, and the mixed NEXOBRID are for use for only one patient and for one application.

NEXOBRID is available as:

- 5 g lyophilized powder (containing 4.85 grams of anacaulase-bcdb) mixed in 50 g gelvehicle, per 2.5% adult BSA, or per 450 cm^2 of treated burn area.

NEXOBRID is for topical use only.

Apply an ointment skin protectant around the treatment area to create an ointment barrier.

Dosage in Adults:

Apply 3 mm thick layer (approximate thickness of a tongue depressor) of NEXOBRID to an area of up to 15% BSA in one application.

If the wound area is more than 15% BSA, apply NEXOBRID in 2 separate sessions (e.g., treat up to 15% BSA in one session and up to 5% BSA in a second session). Apply the second application of NEXOBRID twenty-four (24) hours after the first application to the same or new burn wound area. The total treatment area must not exceed 20% BSA (40 grams of NEXOBRID lyophilized powder) across two treatment sessions.

Dosage in Paediatric Patients 0 to < 6 Years of Age:

Apply 3 mm thick layer (approximate thickness of a tongue depressor) of NEXOBRID to an area of up to 10% BSA in one application.

Dosage in Paediatric Patients 6 to 17 Years of Age:

Apply 3 mm thick layer (approximate thickness of a tongue depressor) of NEXOBRID to an area of up to 15% BSA in one application.

Preparation of Patient and Burn Wound Treatment Area

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

Use pain management as practiced for an extensive dressing change of burn wounds 15 minutes prior to all NEXOBRID-related procedures.

Prepare the wound area as follows:

1. 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 the gel and prevent eschar removal by it.
2. Apply a dressing soaked with an antibacterial solution to the treatment area for at least 2 hours.
3. Ensure the wound bed is clear of any remnants of topical agents.
4. Apply an ointment skin protectant (e.g., petrolatum) 2 to 3 cm outside of the treatment area to create an ointment barrier.
5. Protect any open wounds and acute wound areas (e.g., laceration, abraded skin and escharotomy incision) with skin protectant ointments or ointment gauze to prevent possible exposure to NEXOBRID and possible irritation and possible bleeding from the wound bed.
6. Avoid applying the ointment to the treatment area itself, as this would impede direct contact of NEXOBRID with the eschar.

Preparation and Application of NEXOBRID

Gather the following supplies prior to NEXOBRID preparation and application. All supplies should be sterile:

- Instrument for mixing (e.g., spatula or tongue depressor)
- Tongue depressor for NEXOBRID application
- 0.9% Sodium Chloride Irrigation
- Occlusive film dressing
- Loose, thick fluffy dressing and bandage

Maintain pain management throughout the application as practiced for an extensive dressing change of burn wounds. At least 15 minutes prior to NEXOBRID application, ensure adequate pain control measures are in place to address NEXOBRID-related pain.

Preparation

Prepare NEXOBRID at the patient's bedside within 15 minutes of the intended application.

Using aseptic technique, mix NEXOBRID lyophilized powder and gel vehicle as follows:

1. Pour the NEXOBRID lyophilized powder into the gel vehicle bottle.
2. Thoroughly mix the NEXOBRID lyophilized powder and gel vehicle using a sterile instrument (e.g., tongue depressor or spatula) until the mixture is uniform. The mixed lyophilized powder and gel vehicle produce NEXOBRID in a final concentration of 8.8% w/w.

Discard NEXOBRID if not used within 15 minutes of preparation, as the enzymatic activity of the product decreases progressively following mixing.

Application

Apply NEXOBRID within 15 minutes of preparation as follows:

1. Moisten the treatment area by sprinkling sterile 0.9% Sodium Chloride Irrigation onto the burn wound.
2. Using a sterile tongue depressor, completely cover the moistened treatment area with the mixed NEXOBRID in a 3 mm thick layer (approximate thickness of a tongue depressor) that completely covers the burn wound area.
3. Cover the treated wound with a sterile occlusive film dressing.
4. Gently press the occlusive film dressing at the area of contact with the ointment barrier to ensure adherence between the occlusive film dressing and the sterile ointment barrier and to achieve complete containment of NEXOBRID on the treatment area. NEXOBRID gel should fill the entire volume of the treatment area, and there should be no visible air under the occlusive film dressing.
5. Cover the dressed wound with a sterile loose, thick, fluffy dressing and secure with a sterile bandage.
6. Leave the dressing and NEXOBRID in place for 4 hours.
7. Discard any unused portions of NEXOBRID.

Removal of NEXOBRID

Removal of this medicinal product 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 gel removal.

Remove NEXOBRID after 4 hours. Gather the following supplies prior to NEXOBRID removal. All

supplies should be sterile:

- Blunt-edged instruments (e.g., tongue depressor)
- Large dry gauze
- Gauze soaked with 0.9% Sodium Chloride Irrigation
- Dressing soaked with an antibacterial solution

Implement and maintain pain management as practiced for an extensive dressing change of burn wounds throughout the following removal procedure:

1. Remove the occlusive film dressing using aseptic technique.
2. Remove the ointment barrier using a sterile blunt-edged instrument.
3. Remove the dissolved eschar from the wound by scraping it away with a sterile blunt-edged instrument.
4. Wipe the wound thoroughly with a large sterile dry gauze, then wipe with a sterile gauze that has been soaked with sterile 0.9% Sodium Chloride Irrigation. Rub the treated area until the appearance of a clean dermis or subcutaneous tissues with pinpoint bleeding.
5. To remove remnants of dissolved eschar, apply a dressing soaked with an antibacterial solution for at least 2 hours.

Second Application of NEXOBRID for Adults

For adults, a second application of NEXOBRID may be applied 24 hours following the first application to either the same area previously treated with NEXOBRID or to a new area. A second application may be considered if:

- The wound area is more than 15% BSA, or
- Multiple wound areas on different body surfaces require two treatments for logistical reasons such as body position, or
- The first application's eschar removal was not complete.

The total treated area must not exceed 20% BSA, inclusive of both applications.

Wound Care after Eschar Removal

Wound care following eschar removal should be based on the healthcare provider's clinical judgement (e.g., observe for spontaneous reepithelization or proceed with autograft).

Monitoring

Monitor patients for signs of local or systemic allergic reactions. If a hypersensitivity reaction occurs, remove NEXOBRID (if applicable) from the treatment area and initiate appropriate therapy.

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 this medicinal product should also 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).

- Potential effects on haemostasis (see above).

Patients with renal or hepatic impairment require careful monitoring.

4.3 CONTRAINDICATIONS

NEXOBRID is contraindicated in patients with:

- Known hypersensitivity to anacaulase-bcdb, bromelain, pineapples, or to any of the other components.
- Known hypersensitivity to papayas or papain because of the risk ofcross-sensitivity.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Burn wounds for which this medicinal product is not recommended

This treatment 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 this medicinal product on perineal and genital burns.

Use in patients with cardiopulmonary and pulmonary disease

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

Use in patients with varicose veins

This medicinal product should be used with caution in areas of varicose veins, to prevent erosion of the veins' wall, and the risk of bleeding.

Facial burn wounds

There are literature reports of successful use of this medicinal product on facial burn wounds. Burn surgeons without experience in using this medicinal product should not start using it on facial burn wounds. This medicinal product 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.

Hypersensitivity Reactions

NEXOBRID-Treated Patients

Serious hypersensitivity reactions, including anaphylaxis, have been reported with postmarketing use of NEXOBRID. If a hypersensitivity reaction occurs, remove NEXOBRID (if applicable) and initiate appropriate therapy.

NEXOBRID is contraindicated in patients with a known hypersensitivity to anacaulase-bcdb, bromelain, pineapples or to any other component of NEXOBRID. NEXOBRID is also contraindicated in patients with known hypersensitivity to papayas or papain because of the risk of cross-sensitivity.

Cross sensitivity with NEXOBRID was also reported in the literature for latex proteins (known as latex-fruit syndrome), bee venom, and olive tree pollen.

Healthcare Providers Preparing and Applying NEXOBRID

Healthcare personnel should take appropriate precautions to avoid exposure when preparing and handling NEXOBRID (e.g., gloves, surgical masks, other protective coverings, as needed). In the event of inadvertent skin exposure, rinse NEXOBRID off with water to reduce the likelihood of skin sensitization.

Pain Management

Eschar removal with NEXOBRID and treatment-related burn wound procedures are painful and require adequate analgesia and/or anesthesia. Pain management should be appropriate for an extensive dressing change of burn wounds. At least 15 minutes prior to NEXOBRID application ensure adequate pain control measures are in place to address NEXOBRID-related pain.

Proteolytic Injury to Non-Target Tissues

NEXOBRID is not recommended for treatment of burn wounds where medical devices (e.g., implants, pacemakers, shunts) or vital structures (e.g., large vessels) could become exposed during eschar removal. Protect any open wounds (e.g., laceration, abraded skin and escharotomy incision) with skin protectant ointments or ointment gauze to prevent bleeding.

Coagulopathy

A 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, a component of NEXOBRID. In vitro and animal data suggest that bromelain can also promote fibrinolysis.

Avoid use of NEXOBRID in patients with uncontrolled disorders of coagulation. Use NEXOBRID with caution in patients on anticoagulant therapy or other drugs affecting coagulation, and 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 ofbleeding.

Use in the elderly

Of the 177 elderly subjects exposed to NEXOBRID for eschar removal in deep partial thickness (DPT) and/or full thickness (FT) thermal burns, 6 (3%) subjects were 65 years or older, and 1 (< 1%) subject was 75 years or older. Clinical studies of NEXOBRID did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

Paediatric use

The safety and effectiveness of NEXOBRID in paediatric patients have been established.

Use of NEXOBRID for paediatric patients is supported by evidence from an adequate and well-controlled trial in paediatric patients, with additional supportive safety, efficacy, and tolerability data in adult patients.

A total of 145 paediatric patients were randomized and 139 (69 NEXOBRID, 70 SOC) were treated in the CIDS study.
The number of patients treated with NEXOBRID in the paediatric CIDS study by age group was:

- Age group 0 to <6 years age: n=41
- Age group 6 to 18 years of age: n=28.

The safety and effectiveness were generally consistent between paediatric age groups and adult patients.

Effects on laboratory tests

Not relevant.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical studies have been conducted to assess the potential for systemic drug interactions.

Medicinal products that affect coagulation

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

CYP2C8 and CYP2C9 substrates

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

Topical antibacterial medicinal products

Topically applied antibacterial medicinal products (e.g. silver sulfadiazine or povidone iodine) may decrease the efficacy of this medicinal product.

Fluorouracil and vincristine

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

ACE inhibitors

Bromelain may enhance the hypotensive effect of ACE inhibitors, causing larger decreases in blood pressure than expected. Blood pressure should be monitored in patients receiving ACE inhibitors.

Benzodiazepines, barbiturates, narcotics and antidepressants

Bromelain may increase drowsiness caused by some medicinal products (e.g., benzodiazepines, barbiturates, narcotics and antidepressants). This should be taken into account when dosing such products.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies were performed to assess the effects of this medicinal product on fertility.

Use in pregnancy – B1

There are no available data on NEXOBRID use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or foetal outcomes.

Animal studies are insufficient to properly assess the potential of NEXOBRID to interfere with embryonal/foetal development (see section 5.3). Since the safe use of NEXOBRID during pregnancy has not yet been established, NEXOBRID is not recommended during pregnancy.

Animal Data

In embryofetal developmental studies in rats and rabbits, intravenous doses up to 4 and 0.1 mg/kg/day NEXOBRID were administered to pregnant rats and rabbits, respectively, during organogenesis. No significant developmental toxicities were observed in these studies. However, severe maternal toxicities were noted and the tolerable maternal exposure levels were much lower compared with the maximum human exposure in clinical setting.

Use in lactation.

There are no data on the presence of anacaulase-bcdb in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXOBRID and any potential adverse effects on the breastfed infant from NEXOBRID or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial experience

Adult Patients:

Studies 1 and 2 evaluated subjects undergoing eschar removal for deep partial thickness (DPT) and/or full thickness (FT) thermal burns [see Clinical Studies (14)]. An integrated analysis of safety data from Studies 1 and 2 compared NEXOBRID (n=177) to standard of care (SOC) (n=149). The SOC treatment included both surgical and non-surgical eschar removal methods.

The mean age of the safety population was 35.6 years; 73% were male; 81% were White, 9% were Black, 6% were other races, and 3% were Asian. Regarding burn etiology, 65% had fire/flame burns, 26% had scald burns, 8% had contact burns, and <1% had burns of other etiology. The mean body surface area (BSA) of wounds that received study treatment was 9.2±5.07%. Mean BSA of all burn wounds was 12.0±6.05%. Of the 177 subjects who were treated with NEXOBRID in Studies 1 and 2, 159 (90%) received one treatment of NEXOBRID, and 18 (10%) received 2 treatments.

Table 1 presents adverse reactions that occurred in occurred in ≥ 1% of subjects in the NEXOBRID arm and at a higher incidence than the SOC arm, up to 3 months following wound closure.

Table 1: Adverse Reactions Reported in ≥1% and Greater Incidence than Standard of Care in NEXOBRID-Treated Adult Patients for Eschar Removal in Deep Partial Thickness and/or Full Thickness Thermal Burns in Studies 1 and 2[a]

	NEXOBRID (N = 177) Patients n (%)	**Standard of Care[b] (N = 149)** Patients n (%)
Pruritus	27 (15)	19 (13)
Pyrexia	21 (12)	13 (9)
Wound complicationc	15 (9)	9 (6.0)
Anemia	11 (6)	8 (5)
Vomiting	9 (5)	4 (3)
Insomnia	8 (5)	6 (4)
Urinary tract infection	7 (4)	1 (1)
Tachycardia	5 (3)	0
Rash	6 (3)	0
Infection	4 (2)	2 (1)
Sepsis	4 (2)	1 (1)
Leukocytosis	3 (2)	1(1)
Hypotension	3 (2)	1 (1)
Hepatic function abnormal	2 (1)	0
Drug hypersensitivity	2 (1)	0
Bacteremia	2 (1)	0
Scar	2 (1)	0
Subcutaneous hematoma	2 (1)	0
Decubitus ulcer	2 (1)	0

[a] During the time period from baseline to 3 months post wound closure
[b] Standard of Care treatment included both surgical and non-surgical eschar removal methods
[c] Wound complication includes skin graft failure, graft loss, graft complication, and wound decomposition

Paediatric Patients:

Study 3 evaluated paediatric subjects undergoing eschar removal for deep partial thickness (DPT) and/or full thickness (FT) thermal burns. A total of 139 subjects (69 NEXOBRID, 70 SOC) were treated in the CIDS study. The SOC treatment included both surgical and non-surgical eschar removal methods. Demographic and baseline characteristics were generally comparable in the safety population between the NEXOBRID and SOC arms. The majority of patients were Caucasian (69.6% NEXOBRID, 68.6% SOC) and males (59.4% NEXOBRID, 68.6% SOC). Mean age was similar in the NEXOBRID (5.89 years) and SOC (5.75 years) arms. The majority of burns in both treatment arms (NEXOBRID and SOC) were due to scald (68.1% and 67.1%). The majority of patients in both treatment groups (NEXOBRID and SOC) had 1 treated wound (71.0% and 80.0%, respectively).

Table 3 presents adverse reactions that occurred in ≥ 1% of subjects in the NEXOBRID arm and at a higher incidence than the SOC arm, up to 3 months following wound closure.

Table 3: Adverse Reactions Reported in ≥1% and Greater Incidence than Standard of Care in NEXOBRID-Treated Paediatric Patients for Eschar Removal in Deep Partial Thickness and/or Full Thickness Thermal Burns in Study 3[a] (CIDS study)

	NEXOBRID (N = 69) Patients n (%)	**Standard of Care[b] (N = 70)** Patients n (%)
Pruritus	9 (13)	7 (10)
Pyrexia	7 (10)	4 (6)
Vomiting	5 (7)	3 (4)
Nausea	3 (4)	2 (3)
Constipation	3 (4)	1 (1)
Nasopharyngitis	3 (4)	1 (1)
Rash	2 (3)	0
Hemoglobin decreased	2 (3)	0
Rhinovirus	2 (3)	0
Ear Infection	2 (3)	0

[a] During the time period from baseline to 3 months post wound closure
[b] Standard of Care treatment included both surgical and non-surgical eschar removal methods

Postmarketing Experience

The following adverse reactions have been identified during post approval use of anacaulase-bcdb. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Hypersensitivity, including anaphylaxis and urticaria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Treatment with anacaulase-bcdb prepared in a powder:gel ratio of 1:5 (0.16g per g of mixed gel) in patients with deep partial- and/or full-thickness burns within the framework of a clinical study did not result in significantly different safety findings when compared to treatment with anaclaulase-bcdb prepared in a powder:gel ratio of 1:10 (0.09 g per 1g of mixed gel).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Preparations for treatment of wounds and ulcers, proteolytic enzymes; ATC code: D03BA03.

Mechanism of action

The mixture of enzymes in NEXOBRID dissolves burn wound eschar. The specific components responsible for this effect have not been identified.

Clinical trials

The efficacy of NEXOBRID for the eschar removal of deep partial thickness (DPT) and full thickness (FT) thermal burns has been investigated in two trials.

Adult patients

Study 1

NEXOBRID was investigated in the DETECT randomized, controlled, assessor-blinded, three-arm study, comparing NEXOBRID, standard of care (SOC), and gel vehicle treatment in subjects with DPT and/or FT thermal burns of 3 - 30% BSA (Study 1, NCT02148705). SOC included both surgical and non-surgical methods for eschar removal per the investigators' discretion. Subjects on the NEXOBRID and gel vehicle arms who had eschar remaining following the topical treatment period were treated with SOC. NEXOBRID was compared to gel vehicle for the incidence of ≥95% eschar removal at the end of the topical treatment period. NEXOBRID was also compared with SOC for the incidence of surgical eschar removal (tangential, minor, avulsion, Versajet and/or dermabrasion excision) and time to eschar removal.

A total of 175 subjects were randomized in a 3:3:1 ratio (NEXOBRID : SOC : gel vehicle) and 169 subjects were treated. The mean age was 41 years, 70% of subjects were male and 30% were female, and 81% were White, 14% were Black or African American, 5% were other races, and 1% were Asian. Seventeen percent of subjects were Hispanic or Latino. Subjects had one or more target wounds (TWs) to be treated for eschar removal. The mean percentage BSA of all TWs per subject was 6.1%. The majority of subjects (82%) had one to two TWs.

The incidence of ≥95% eschar removal at the end of the topical treatment period for subjects in the NEXOBRID and gel vehicle groups is shown in Table 2.

Table 2: Incidence of ≥95% Eschar Removal at the End of the Topical Treatment Period in NEXOBRID - or Gel Vehicle - Treated Subjects with Deep Partial Thickness and/or Full Thickness Thermal Burns (Study 1; DETECT)

NEXOBRID (N=75)	Gel Vehicle (N=25)	Treatment Difference (95% Confidence Interval)
93% (70/75)	4% (1/25)	89% (74%, 96%)

The incidence of surgical eschar removal (tangential, minor, avulsion, Versajet and/or dermabrasion excision) and time to ≥95% eschar removal for the NEXOBRID and SOC groups are shown in Table 3.

Table 3: Incidence of Excision for Eschar Removal in NEXOBRID- or SOC-Treated Subjects with Deep Partial Thickness and/or Full Thickness Thermal Burns (Study 1; DETECT)

NEXOBRID (N=75)	SOC (N=75)	Treatment Difference (95% Confidence Interval)
4% (3/75)	72% (54/75)	-68% (-78%, -56%)

SOC = standard of care

The median time to eschar removal was 1 day on the NEXOBRID arm and 3.8 days on the SOC arm.

The estimated median time to ≥95% wound closure for all TWs on a subject was 31 days for the NEXOBRID arm and 36 days for the SOC treatment arm. Subjects were not evaluated frequently enough after achieving ≥95% wound closure to adequately assess time to 100% wound closure.

Study 2

NEXOBRID was investigated in a multicenter, open-label, randomized, two-arm study, comparing NEXOBRID to SOC treatment in subjects with DPT and/or FT thermal burns of 5-24% BSA (Study 2; NCT00324311). SOC included both surgical and non-surgical methods for eschar removal per the investigators' discretion. The study enrolled 182 subjects. The first subject at each site (26 subjects) was not randomized and was treated with NEXOBRID. The remaining 156 subjects were randomized to NEXOBRID or SOC. The efficacy assessments were analyzed on DPT burns only.

Demographics were similar across both arms. The mean age was 29.9 years. Approximately 80% of the study subjects were adults (≥18 years), 74% were male and 26% were female, 82% were White, 7% were other races, 6% were Black, and 5% were Asian.

The incidence of surgical eschar removal (tangential, minor, avulsion, Versajet and/or dermabrasion excision) for the NEXOBRID and SOC groups is shown in Table 4.

Table 4: Incidence of Excision of Eschar Removal of Deep Partial Thickness Wounds in Patients with Thermal Burns (Study 2)

	NEXOBRID N=106 Wounds in 49 Subjects[a]	SOC N=88 Wounds in 48 Subjects[a]	Treatment Difference (95% Confidence Interval)
Incidence of excision for eschar removal (per wound)[b]	15% 16/106 wounds	63% 55/88 wounds	-47% (-59%, -34%)
Incidence of excision for eschar removal (per subject)[b,c]	22% 11/49 subjects	77% 37/48 subjects	-55% (-71%, -38%)

SOC = standard of care

[a] Analysis population includes only patients with at least one wound that was entirely DPT

[b] Surgical eschar removal procedures include (tangential, minor, avulsion, Versajet and/or dermabrasion excision)

[c] Assessment per subject was an exploratory analysis

In randomized subjects, the estimated median time to ≥95% wound closure was 33 days for the NEXOBRID arm and 24 days for the SOC treatment arm. Subjects were not evaluated frequently enough after achieving ≥95% wound closure to adequately assess time to 100% wound closure.

Pediatric Patients

Study 3: CIDS

NEXOBRID was investigated in the CIDS randomized, controlled, two arm study comparing NEXOBRID and standard of care (SOC) treatment in subjects with DPT and/or FT thermal burns of ≥1% - 30% BSA (Study 3, NCT02278718). SOC included both surgical and nonsurgical methods for eschar removal per the investigator's discretion. Subjects on the NEXOBRID arm who had eschar remaining following the topical treatment period were treated with SOC.

NEXOBRID was compared with SOC for the time to eschar removal and for the incidence of surgical eschar removal (tangential, minor, avulsion, Versajet and/or dermabrasion excision).

A total of 145 subjects were randomized in a 1:1 ratio (NEXOBRID:SOC) and 139 subjects were treated. The mean age was approximately 6 years, 62% were male and 38% were female, and 70% were White, 23% were Asian, 7% were Hispanic, 4% were Black or African American, and 3% were other races. Subjects had one or more target wounds (TWs) to be treated for eschar removal. The mean percentage BSA of all TWs per subject was 5.6%. The majority of patients in both treatment groups (NEXOBRID and SOC) had 1 TW (71.0% and 80.0%).

The median time to complete eschar removal is shown in Table 5.

TABLE 5: TIME TO COMPLETE ESCHAR REMOVAL (MAIN ANALYSIS), ESTIMATED MEDIAN TIME FOR NEXOBRID VS SOC (STUDY 3; CIDS)

Treatment	Median (Days)	Lower 95% Confidence Bound	Upper 95% Confidence Bound
NEXOBRID (72 patients)	0.99	0.88	1.04
SOC (73 patients)	5.99	2.71	9.84

The incidence of surgical eschar removal (tangential, minor, avulsion, Versajet and/or dermabrasion excision) is shown in Table 6.

Table 6: Incidence of Surgical Excision for Eschar Removal for NEXOBRID vs SOC (Study 3; CIDS)

n	Incidence Rate (NexoBrid/SOC)	Odds Ratio	p-value	Lower 95% Confidence Bound	Upper 95% Confidence Bound
72 NEXOBRID 73 SOC	6/72 (8.33%)/ 47/73 (64.38%)	0.025	<0.0001	0.007	0.090

The estimated median time to ≥95% wound closure for all target wounds on a subject was 32 days for the NEXOBRID arm and 41 days for the SOC treatment arm. The estimated median time reach 100% wound closure on a target wound level was 44 days for NexoBrid arm and 50 days for the SOC arm.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

For adults, topically applied NEXOBRID to deep partial and full thickness burn wounds is rapidly absorbed, with median serum Tmax of 4 hours (during the treatment application). Systemic exposure (i.e., AUC) of bromelain, a component of anacaulase-bcdb is correlated with the size of the treated area and NEXOBRID dose, but not the depth of the burn wound.

Similar to adults, for paediatric patients, topically applied concentrations of NEXOBRID increase relatively rapidly corresponding to the period of NexoBrid topical administration, with median Tmax values between 2 to 4 hours.

Excretion

A majority of adults and paediatric patients had no quantifiable serum concentrations after 72 hours. The mean ± SD terminal half-life of bromelain, a component of anacaulase-bcdb, is 12 ± 4.4 hours.

In adult patients, Cmax and the dose-normalized Cmax values after the first and second application (mean dosing interval of 17 hours) are comparable and only slight accumulation (less than 2-fold difference) is seen in AUC0-4 and AUC0-4 dose-normalized levels after the second application, compared to the first application. No paediatric subjects for which there are PK data had 2 applications of NEXOBRID.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Anacaulase-bcdb was not genotoxic in a bacterial reverse mutation assay and an in vitro mammalian chromosome aberration assay.

Carcinogenicity

Carcinogenicity or fertility studies have not been conducted with anacaulase-bcdb.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder

Ammonium sulfate
Acetic Acid

Gel

Carbomer 980
Dibasic sodium phosphate
Sodium hydroxide
Water for injections

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.1.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store and transport refrigerated (2°C-8°C).

Store upright to keep the gel at the bottom of the bottle and in the original package to protect from light.

Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

5 g powder in a vial (glass type II) sealed with a rubber (bromobutyl), stopper and covered with a cap (aluminium), and 50 g gel in a bottle (borosilicate, glass type I), sealed with a rubber stopper and covered with a screw cap (tamper-proof polypropylene).

Pack size of 1 vial of powder and 1 bottle of gel.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The drug substance in NEXOBRID, anacaulase-bcdb, is a mixture of proteolytic enzymes extracted from the stems of pineapple plants (Ananas comosus [L.] Merr.) that has been sterile filtered and lyophilized. The drug substance, anacaulase-bcdb, is composed mainly (80% to 95% w/w) of the proteins: stem bromelain, ananain, jacalin-like lectin, bromelain inhibitors, and phytocystatin inhibitor; and saccharides, as both free monosaccharides and the N-linked glycan of stem bromelain, and small molecule metabolites.

CAS number

68917-26-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Nexo Pharmaceuticals PTY. Ltd
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Kenmore East QLD 4069
Australia

0488 032 096

9 DATE OF FIRST APPROVAL

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information