EU Risk Management Plan (RMP) for NEXOBRID (concentrate of proteolytic enzymes enriched in bromelain)

RMP version to be assessed as part of this application:

RMP version number:	9.4
Data lock point for this RMP:	17 December 2021
Date of final sign off:	10 November 2023

Rationale for submitting an updated RMP:

This update is submitted together with the type II variation procedure proposing an extension of indication for use of NexoBrid, including the use in paediatric population.

Summary of significant changes in this RMP:

- **Part I Product(s) Overview**

Indication for use and posology were updated to reflect on the paediatric population.

- **Part II Safety Specification**

Module SI was revised to reflect on the epidemiology of burn injuries in the paediatric population.

Module SII was revised to include the key nonclinical safety findings from the repeat-dose toxicity study in juvenile farm pigs.

Clinical trial exposure presented in Module SIII was revised to include the paediatric patient population.

Module SVII was amended with the data supporting the use of NexoBrid in the paediatric population. Additionally, Module SVII was amended in line with the requirements set out in the completed procedure EMEA/H/C/002246/II/0057.

All changes made to the RMP were reflected in Part VI.

Other RMP versions under evaluation:

RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:

RMP version number:	8.2
Approved within procedure:	EMEA/H/C/002246/II/0057
Date of approval (opinion date):	30 March 2023

QPPV name: Jana Mlada, MD

The content of this RMP has been reviewed and approved by the marketing authorisation select holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ATC	Anatomical Therapeutic Chemical classification system
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSR	Clinical Study Report
CYP	Cytochrome P450
CYP2C8	Cytochrome P450 isoform 2C8
CYP2C9	Cytochrome P450 isoform 2C9
DGD	Debrase/NexoBrid gel dressing
DPT	Deep partial thickness
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FPS-R	Face-Pain Scale-Revised
FT	Full-thickness
GVP	Good Pharmacovigilance Practice
HIV	Human Immunodeficiency Virus
IBD	International Birth Date
INN	International Nonproprietary Name
ISS	Integrated Summary of Safety
NOAEL	No-Observed-Adverse-Effect Level
OR	Odds ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PCEs	Polychromatic erythrocytes
PIP	Paediatric Investigation Plan
PL	Package Leaflet
PSUR	Periodic Summary Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA query

SOC	Standard of care
TBSA	Total body surface area
TTCWC	Time to complete wound closure
UK	United Kingdom
US	United States
WBC	White blood cell
WHO	World Health Organization

PART I: Product(s) Overview

Active Substance(s) (INN or Common Name)	Concentrate of proteolytic enzymes enriched in bromelain (bromelains)
Pharmacotherapeutic Group(s) (ATC Code)	Proteolytic enzymes (D03BA03)
Marketing Authorisation Holder	MediWound Germany GmbH
Medicinal Product(s) to Which This RMP Refers	2
Invented Name(s) in the European Economic Area (EEA)	NexoBrid
Marketing Authorisation Procedure	Centralised procedure
Brief Description of the Product	**Chemical Class** NexoBrid consists of a mixture of proteolytic enzymes from the stem of *Ananas comosus* (pineapple plant). The major constituent is stem bromelain.
	Summary of Mode of Action The mixture of enzymes in NexoBrid dissolves burn wound eschar. The specific components of the mixture responsible for this effect have not been identified.
	Important Information about its Composition None
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	**Current:** NexoBrid is indicated for removal of eschar in adults with deep partial- and full-thickness thermal burns
	Proposed: NexoBrid is indicated in all age groups for removal of eschar in patients with deep partial- and full-thickness thermal burns
Dosage in the EEA	**Current:** – **2 g powder and gel for gel:** 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. NexoBrid should not be applied to more than 15% TBSA. – **5 g powder and gel for gel:** 5 g NexoBrid powder in 50 g gel is applied to a burn wound area of 2.5% TBSA of an adult, with a gel layer thickness of 1.5 to 3 mm. NexoBrid should not be applied to more than 15% TBSA.

	Proposed: ***Adults*** 2 g powder in 20 g gel is applied to 1% Total Body Surface Area (TBSA) that corresponds to approximately 180 cm^2 of an adult, with a gel layer thickness of 1.5 to 3 mm. 5 g powder in 50 g gel is applied to 2.5% TBSA that corresponds to approximately 450 cm^2 of an adult, with a gel layer thickness of 1.5 to 3 mm. NexoBrid should not be applied to more than 15% TBSA. ***Children and adolescents (from birth to 18 years of age)*** For paediatric patients aged 4-18 years, NexoBrid should not be applied to more than 15% TBSA. For paediatric patients aged 0-3 years, NexoBrid should not be applied to more than 10% TBSA.
Pharmaceutical Form(s) and Strength(s)	**Current:** Powder and gel for gel. The powder is off-white to light tan. The gel is clear and colourless. – **2 g powder and gel for gel:** One vial contains 2 g of concentrate of proteolytic enzymes enriched in bromelain, corresponding to 0.09 g/g concentrate of proteolytic enzymes enriched in bromelain after mixing (or 2 g/22 g gel). – **5 g powder and gel for gel:** One vial contains 5 g of concentrate of proteolytic enzymes enriched in bromelain, corresponding to 0.09 g/g concentrate of proteolytic enzymes enriched in bromelain after mixing (or 5 g/55 g gel)
	Proposed: Not applicable
Is/Will the Product be Subject to Additional Monitoring in the EU?	No

ATC = anatomical therapeutic chemical; EEA = European Economic Area; EU = European Union; INN = international non-proprietary name; RMP = Risk Management Plan.

PART II: Safety Specification

PART II: Module SI - Epidemiology of Indication(s) and Target Population(s)

Deep Partial- and Full-Thickness Thermal Burns

Incidence/Prevalence:

Severe burn injuries requiring medical attention affected nearly 11 million people globally in 2004, representing the fourth leading cause of major injury worldwide (Stylianou et al, 2015; World Health Organization, 2018). Burns are the fifth most common cause of non-fatal childhood injuries (World Health Organization, 2018).

Exact data showing the incidence/prevalence of burn injuries in the EU/EEA are not available. The annual incidence of severe burn injuries was estimated to lie between 0.2 and 2.9 per 10,000 European inhabitants based on the systemic review of studies published between 1985 and 2009 and focused on severe burn injuries requiring hospitalisation in Europe (Brusselaers et al, 2010). Children are reported to account for almost half of all burns and scalds in European hospitals (Brusselaers et al, 2010).

Scandinavian data show the incidence of burn injuries requiring medical attention at 0.4% per year (Akerlund et al, 2007). The rate of hospital admissions for burn injuries was 15.5/100,000/year in 2007 in Norway (Onarheim et al, 2009).

Demographics of the Population in the Authorised Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Condition:

Patients admitted to hospital for burn injury showed a double-peaked age distribution with the first maximum at age group of 0 to 4 years and the other lower maximum in early adulthood (20 to 25 years; up to 35 years of age in certain regions) (den Hertog et al, 2000; Chien et al, 2003; Akerlund et al, 2007).

The most common age for a child to suffer a burn injury is 1 year, with ten times as many burns and scalds as any school year age group (Battle et al, 2016).

The median age of the children was 2 years in the retrospective study conducted in the United Kingdom (UK) and including data from a 7-year period. As in previous research, more male children presented to the emergency department with scalds and burn injuries than female (Battle et al, 2016).

Elderly people were found at increased risk for burn injury in studies from the United States (US) and the Netherlands (den Hertog et al, 2000; Bessey et al, 2006) but not from Sweden (Akerlund et al, 2007).

Burn injuries in the EU are more prevalent in men than women. The analysis of 24,538 burn cases requiring hospitalisation in Sweden between 1987 and 2004 showed a male:female ratio of 2.23:1 (i.e., 69% of men and 31% of women) and men predominated in all age groups analysed (Akerlund et al, 2007). This finding is supported by the data from other studies conducted in Europe (Portugal, Norway, England/Wales) (da Silva et al, 2003; Onarheim et al, 2009; Stylianou et al, 2015) or worldwide, including Israel (Haik et al, 2007), China or Taiwan—approximately 67% of hospitalised burn patients in Taiwan represented men (Chien et al, 2003).

The slight predominance of women in burn injuries is reported from the low- and middle-income countries (World Health Organization, 2018). People living in low- and

middle-income countries are at higher risk for burns than people living in high-income countries. Within all countries, however, burn risk correlates with socioeconomic status (World Health Organization, 2018).

– **Risk Factors**

Worldwide data show that people living in low- and middle-income countries are at increased risk of burn injuries than those living in high-income countries. Risk of burn injuries further directly correlates with the socioeconomic status (World Health Organization, 2018).

There are other general risk factors for burn injuries, including (World Health Organization, 2018):

– occupations that increase exposure to fire
– poverty, overcrowding, and lack of proper safety measures
– placement of young girls in household roles such as cooking and care of small children
– cooking pots on the floor, number of cooking pots and abundant use of cooking oils and boiling water that are prone to spill over or people can step into them
– underlying medical conditions, including epilepsy, peripheral neuropathy, and physical and cognitive disabilities
– alcohol abuse and smoking
– easy access to chemicals used for assault (such as in acid violence attacks)
– use of kerosene (paraffin) as a fuel source for non-electric domestic appliances
– inadequate safety measures for liquefied petroleum gas and electricity.

Social deprivation and child maltreatment has been demonstrated to be a risk factor for childhood accidents, including burn injuries, and deaths (Battle et al, 2016; World Health Organization, 2018). However, a retrospective study from the UK showed that child maltreatment was suspected in only 1% of cases from this region (Battle et al, 2016).

Main Existing Treatment Options:

Surgical excision with tangential knives and/or hydro surgery represents the standard of care for burn eschar removal in the EU (Hirche et al, 2020).

Enzymatic debridement with NexoBrid represent an additional tool in the armamentarium and a useful alternative to operative eschar removal.

Enzymatic debridement shows its strength in mid-to-deep dermal burns with mixed patterns to preserve as much viable dermis as possible for improved functional outcome. Its application in full-thickness (FT) burns can be regarded as a useful indication, to reduce the time to complete eschar removal (Hirche et al, 2020).

The updated European consensus guidelines on eschar removal by NexoBrid identified areas, where debridement with NexoBrid can bring advantages over standard of care surgical methods, including eschar removal of facial, perineal or genital burns (Hirche et al, 2020). The use of NexoBrid on hand burns (including palm) and sole burns might be indicated in selected patients.

Other techniques available for eschar removal include enzymatic debridement with streptokinase, streptodornase or bacterial-derived proteases (Heitzmann et al, 2020), autolytic methods using hydrocolloids and hydrogels, or biologic methods, based on the use of the larvae *Lucilia sericata*.

Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity:

Non-fatal burn injuries represent a worldwide leading cause of morbidity, including prolonged hospitalisations, disfigurement and permanent disability (World Health Organization, 2018). Burn victims are often burdened by rejection or stigmatisation (World Health Organization, 2018).

Children have been shown more prone to accidents, including thermal injury, than adults and in many countries constitute the majority of burn victim population (Vloemans et al, 2014). Boys under 5 years of age living in low- and middle-income countries of the WHO Eastern Mediterranean Region are almost 2 times as likely to die from burns as boys living in the WHO European Region (World Health Organization, 2018).

Burns in children exhibit the same pathophysiological responses as adults but with modifications due to several factors. These factors include smaller size, thinner skin, greater heat loss, and differences in blood volume (Sheridan et al, 2000), as well as altered emotional and psychological responses to injury, including burns. The overall mortality rate among patients (adult and paediatric) with burns is approximately 3% to 5% (Meshulam-Derazon et al, 2006; Akerlund et al, 2007; Haik et al, 2007; Sanchez et al, 2007). The mortality rate among hospitalised patients (adult and paediatric) with severe burn injuries in the EU was reported to lie between 1.4% and 18% (maximum 34%) (Brusselaers et al, 2010).

Increased mortality and/or morbidity has been associated with advancing age, larger TBSA (the mortality increases considerably above a TBSA of 20%), diabetes, severe immunodeficiency as well as other underlying conditions such as renal or liver disease, or pulmonary circulatory disorders (Ryan et al, 1998; Aldemir et al, 2005; Church et al, 2006; Haik et al, 2007; Thombs et al, 2007; Brusselaers et al, 2010). The presence of smoke inhalation may increase mortality risk 9-fold (Meshulam-Derazon et al, 2006).

Important Co-Morbidities:

There is no specific co-morbidity associated with burn injury but pre-existing co-morbidities may significantly impact the outcomes of burn injuries, especially in the elderly (Costa Santos et al, 2017).

The most common co-morbidities reported in burn patients in Europe and the US include the following (Thombs et al, 2007; Costa Santos et al, 2017):

- Chronic obstructive pulmonary disease (COPD)
- Cardiac disease
- Hypertension
- Diabetes
- Mental disease
- Neurologic disease
- Alcohol abuse and smoking
- Obesity
- Renal and liver diseases

PART II: Module SII - Non-Clinical Part of the Safety Specification

Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage:

Toxicity

Single and Repeat-Dose Toxicity

In a single dose study in minipigs, the effect of delivering the NexoBrid solution (under its development code name Debrase[1]) as a 2-hour infusion (24, 48 or 96 mg/kg) was investigated in one animal per sex and dose. The 96 mg/kg dose was associated with death or early sacrifice due to haemorrhaging, whereas the lower doses were well tolerated with slight transient elevations in coagulation parameters.

The systemic toxicity of repeat dosing was assessed in a minipig study where 15 minutes slow-bolus intravenous doses of up to 12 mg/kg were administered 3 times a week for 2 weeks. This treatment was well tolerated for the first four injections but clinical signs including convulsions, decreased activity, ataxia, salivation, laboured breathing, and defecation were first observed beginning on Day 10 in all NexoBrid dose groups and was present throughout the remaining period of treatment. Histopathological changes consisted primarily of haemorrhage in several tissues.

Similar findings were also observed in a repeat-dose study conducted in juvenile farm pigs, where the animals received doses up to 12 mg/kg, administered 3 times a week for 2 weeks by slow-bolus intravenous injection. Following the fifth intravenous dose on Day 10, convulsions, reddening of the skin, activity decreased, breathing difficult, and ataxia were noted in all NexoBrid dose groups and persisted throughout the remaining period of treatment. The possibility of an allergic/anaphylactoid type reaction in the treated animals was raised, and the second set of animals was pre-treated with antihistamines to see if the symptoms could be averted. Pre-treatment with antihistamines, though slightly decreasing the incidence of convulsions in the lower dose groups did not ameliorate the adverse clinical findings. Treatment-related histological changes included haemorrhage in multiple tissues, pancreatic acinar cell degeneration and single cell necrosis, as well as lymphoid depletion in the thymic cortex. Prolongation in the activated partial thromboplastin time (aPTT) and prothrombin time was observed at all dose levels in both sexes relative to controls. The haemorrhagic events may be correlated to the changes in the coagulation parameters observed (prolongation of prothrombin time and aPTT and decrease in fibrinogen).

– Relevance to Human Use: The preclinical single and repeat-dose toxicity studies have shown a potential of NexoBrid to interfere with the clotting system after intravenous administration. The observation that haemorrhage was observed already at 4 mg/kg in this repeat dose study whereas higher doses were found to be tolerable after single dosing (12 mg/kg with slow bolus and possibly 48 mg/kg with slow infusion) suggests that the effect on the clotting system is cumulative when dosing occurs every other to every third day. Based on these findings, the increased tendency to bleeding represents an important potential risk of NexoBrid and is further discussed in PART II: Module SVII. However, there has been no indication of an increased tendency to bleeding due to coagulation abnormalities or at the site of debridement during the clinical development of NexoBrid.

[1] Beside the development code name Debrase, NexoBrid was also referred to as Debrase/NexoBrid Gel Dressing or DGD in the clinical trials conducted by MediWound. Only NexoBrid is used throughout the document.

Developmental Toxicity

The pivotal developmental toxicity studies conducted in rats and rabbits showed no signs of embryo-foetal toxicity of NexoBrid in the absence of clear maternal toxicity.

It was observed that rabbits were particularly sensitive to systemically administered NexoBrid, resulting in maternal no-observed-adverse-effect level (NOAEL) of 0.01 mg/kg. However, even the rat study revealed maternal toxicity in the absence of embryo-foetal toxicity with the maternal NOAEL of 0.5 mg/kg/day. Thus, the highest doses investigated in both the rat and rabbit developmental study were considerably lower than those maximally reported in the clinical setting.

– Relevance to Human Use: The sensitivity of rats/rabbits to systemically administered NexoBrid did not allow to investigate the true potential of NexoBrid to interfere with embryo-foetal development in humans.

Genotoxicity

No mutagenic activity of NexoBrid was observed in the Ames *Salmonella* assay with or without pre-incubation or in the presence or absence of an S9 metabolic activation system. No treatment related increase in chromosomal aberrations were observed when investigated in Chinese hamster V79 cells in the presence and absence of a metabolic activation system.

Increased frequency of micronuclei in bone marrow polychromatic erythrocytes (PCEs) was observed in *in vitro* micronuclei assay in oral high dose (2,000 mg/kg) administered mice females, statistically significant compared to controls. The micronuclei incidence in control females showed a clearly lower mean micronuclei frequency than the recent historical controls (3.2 micronucleated PCEs/2,000 PCEs) as well as the control males within the NexoBrid study who normally have the same frequency of micronucleated PCEs as the female animals. The isolated statistically significant finding is not considered to have any biological relevance.

– Relevance to Human Use: Based on the findings from a standard battery for genotoxicity testing, NexoBrid does not show a relevant genotoxic potential.

Other Toxicity-Related Information or Data

Interactions

The *in-vitro* testing of NexoBrid (mainly consisting of stem bromelain) in human liver microsomes showed complete or near complete loss of activity of cytochrome P450 (CYP) isozymes 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 at all concentrations tested. In human hepatocytes, NexoBrid showed little or no evidence of time-dependent and/or concentration-dependent inhibition of CYP2C9 or CYP1A2, CYP2B6, CYP2C19, CYP2D6 or CYP3A4/5.

In the second set of experiments using human hepatocytes, there was little to no clear evidence of time-dependent and/or concentration-dependent inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 by NexoBrid. CYP2C8 and CYP2D9 time-dependent inhibition with IC_{50} of 30 µg/mL and 129 µg/mL, respectively, was shown in human hepatocytes with and without correlation to the cell viability.

– Relevance to Human Use: NexoBrid *in vitro* metabolism inhibition experiments using human hepatocytes showed both a direct and a time-dependent inhibition of CYP2C8/2C9 of unknown clinical relevance.

Local Tolerance

Severe irritation and pain were noted following the application of NexoBrid to abraded skin of minipigs in the local tolerance studies. The product was applied dermally to the minipigs at 10%, 20% or 30% concentration (to intact and abraded skin). The concentration 20% and 30% caused significant behavioural responses interpreted as pain. Irritation and erythema were evident at all test concentrations and abrasion and scabbing of intact skin was seen at the application site. Microscopic examination indicated bacterial colonies, oedema, hyperkeratosis, epidermal hyperplasia, subacute inflammation with rare cases of ulceration. The changes were reversible.

The findings from local tolerability studies suggest that there is a potential for reversible local reactions when NexoBrid is applied on intact skin and that contact with abraded skin could be irritating and painful.

– Relevance to Human Use: The study in minipigs have shown that NexoBrid has an irritant potential when applied to intact or abraded skin. Severe irritation represents an important potential risk of NexoBrid, while pain is an important identified risk associated with the therapy (refer to PART II: Module SVII).

PART II: Module SIII - Clinical Trial Exposure

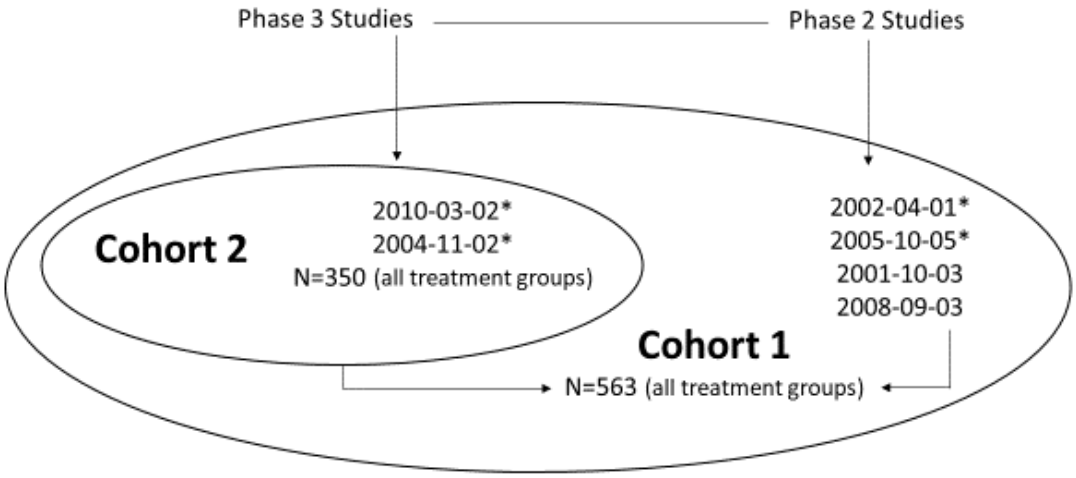
SIII.1 Adult Population

The initial marketing authorisation application (MAA) in the EU for NexoBrid in the adult population was supported by the data from 3 prospective well-controlled studies MW2002-04-01, MW2004-11-02 and MW2005-10-05, and additional data from studies MW2001-10-03 and MW2008-09-03, including overall 208 study subjects exposed to NexoBrid. Additionally, data from the retrospective data collection 35-98-910 were part of the initial MAA, including 154 study subjects.

The updated pooled safety analysis set in the adult population comprises all patients (adult and paediatric) who received study treatment with NexoBrid, standard of care (SOC), or placebo (i.e., gel vehicle) in any of the six phase II and III studies (i.e., MW2010-03-02 [DETECT], MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03) (Figure 1). Studies MW2010-03-02 (DETECT), MW2001-10-03, MW2002-04-01, and MW2005-10-05 include adult subjects only, while studies MW2004-11-02 and MW2008-09-03 include both adult and paediatric subjects.

The primary focus of the updated pooled safety analysis set in adult population is the phase III cohort (Cohort 2), which contains pooled data from the two pivotal phase III studies, MW2010-03-02 (DETECT) and MW2004-11-02. Cohort 1 is comprised of all six (phase II and III) studies (Figure 1).

Figure 1: NexoBrid Clinical Study Safety Cohorts for Pooled Safety Analysis Set



* Studies included in wound closure analysis
Studies MW2004-11-02 and MW2008-09-03 included adult and paediatric study subjects.
Source: eCTD Module 2.7.4

The subject exposure to study treatment in the pooled safety analysis set per study cohorts is provided in Table 1 and Table 2. These tables include data pertinent to adult population as well as paediatric subjects treated in studies MW2008-09-03 (N = 3) and MW2004-11-02 (N = 17).

SIII.2 Paediatric Population

The Paediatric Investigational Plan (PIP) for NexoBrid originally included 3 clinical studies:

- follow-up non-interventional study MW2012-01-02 of paediatric patients treated with NexoBrid in a phase III study MW2004-11-02 (therefore, no paediatric patient has been treated in study MW2012-01-02)
- pivotal phase III study MW2012-01-01 (CIDS)
- phase III study MW2014-01-01, which was later removed from the PIP and the long-term follow-up of at least 2.5 years after wound closure was incorporated in study MW2012-01-01 (CIDS).

Additionally, the retrospective data collection 35-98-910 and phase II study MW2008-09-03 supporting the initial MAA in adult population included overall 80 paediatric patients. Therefore, the clinical development programme for NexoBrid in the paediatric population includes data on 166 paediatric patients from 5 clinical studies (MW2012-01-01 [CIDS], MW2004-11-02, 35-98-910, MW2008-09-03, and MW2012-01-02 [long-term follow-up data]).

The primary evidence on safety of NexoBrid in paediatric population is based on the data from the well-controlled pivotal phase III study MW2012-01-01 (CIDS), with the supporting evidence from the pooled paediatric population, across all clinical studies of NexoBrid conducted in paediatric subjects (Studies MW2012-01-01 [CIDS], MW2008-09-03, and MW2004-11-02), pooled adult population (including data from adult subjects in Studies MW2001-10-03, MW2002-04-01, MW2008-09-03, MW2004-11-02, MW2005-10-05, and MW2010-03-02 [DETECT]), and overall pooled population (adult and paediatric).

The subject exposure to study treatment in paediatric population from the pivotal study MW2012-01-01 (CIDS) is provided in Table 3 and Table 4, while the subject exposure to study treatment in pooled paediatric population is provided in Table 5 and Table 6.

The subject exposure in adult pooled population is provided in Table 7 and Table 8, while the overall pooled population (adult and paediatric) is provided in Table 9 and Table 10.

Full information on the clinical development programme for NexoBrid is provided in the eCTD Module 2.5 Clinical Overview and Module 2.7.4 Summary of Clinical Safety (Addendum).

Table 1: Cumulative Patient Exposure to Study Drug and Follow-up Duration by Study Cohort (Pooled Safety Analysis Set)

Analysis Parameter	Cohort 2 [a] (N = 350)			Cohort 1 [a] (N = 563)		
	NexoBrid (N = 177)	Standard of Care (N = 149)	Gel Vehicle (N = 24)	NexoBrid (N = 300)	Standard of Care (N = 195)	Gel Vehicle (N = 68)
Dose (g)						
n	160	0	24	278	0	65
Mean (SD)	16.6 (10.33)	-	216.5 (191.78)	15.7 (10.80)	-	156.7 (144.67)
Median	14.0	-	135.0	12.0	-	100.0
Min, Max	2, 60	-	30, 720	2, 60	-	20, 720
Follow-up in PY [b]						
Total PY	61.89	50.22	8.62	90.11	61.86	20.57
1 application	54.03	-	-	75.4	-	-
2 applications	7.86	-	-	14.71	-	-
TBSA ≤ 15%	55.75	45.53	8.15	81.62	57.16	20.11
TBSA > 15%	6.14	4.69	0.47	8.5	4.69	0.47
Follow-up in Months [b]						
Mean (SD)	4.2 (1.72)	4.0 (1.39)	4.3 (0.94)	3.6 (1.83)	3.8 (1.47)	3.6 (1.43)
Median	4.2	4.1	4.2	3.9	3.9	3.9
Min, Max	0, 15	0, 9	3, 7	0, 15	0, 9	0, 7

Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03
Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; n = number of patients; N = total number of patients; SD = standard deviation; PY = person-years; TBSA = total burn surface area
[a] Cohort 2 study MW2004-11-02 and Cohort 1 study MW2008-09-03 included both adult and paediatric subjects.
[b] PY of follow-up and follow-up duration in months show data for the acute phase (i.e., up to 3 months after complete wound closure of all target wounds).
Source: ISS, Tables 14.1.3.3.2 and 14.1.3.3.1a

Table 2: Baseline Demographics and Disease Characteristics by Study Cohorts (Pooled Safety Analysis Set)

Analysis Parameter	Cohort 2 [a] (N = 350)			Cohort 1 [a] (N = 563)		
	NexoBrid (N = 177)	Standard of Care (N = 149)	Gel Vehicle (N = 24)	NexoBrid (N = 300)	Standard of Care (N = 195)	Gel Vehicle (N = 68)
Age (Years)						
Mean (SD)	36.8 (15.57)	34.6 (15.75)	41.0 (17.65)	36.4 (15.16)	35.3 (15.05)	37.8 (13.56)
Median	36.7	32.1	36.8	35.3	34.2	36.2
Min, Max	4, 76	5, 73	18, 70	4, 76	5, 73	18, 70
Age Group (Years), n (%)						
< 18	17 (9.6)	16 (10.7)	0	20 (6.7)	16 (8.2)	0
18 to 64	153 (86.4)	128 (85.9)	20 (83.3)	269 (89.7)	174 (89.2)	64 (94.1)
³ 65	7 (4.0)	5 (3.4)	4 (16.7)	11 (3.7)	5 (2.6)	4 (5.9)
Gender, n (%)						
Female	50 (28.2)	33 (22.1)	10 (41.7)	80 (26.7)	46 (23.6)	21 (30.9)
Male	127 (71.8)	116 (77.9)	14 (58.3)	220 (73.3)	149 (76.4)	47 (69.1)
Race, n (%)						
Asian	7 (4.0)	4 (2.7)	0	38 (12.7)	20 (10.3)	12 (17.6)
Black	12 (6.8)	18 (12.1)	3 (12.5)	23 (7.7)	22 (11.3)	12 (17.6)
Caucasian	141 (79.7)	113 (75.8)	20 (83.3)	207 (69.0)	138 (70.8)	42 (61.8)
Middle Eastern	7 (4.0)	4 (2.7)	0	20 (6.7)	4 (2.1)	0
Other	10 (5.6)	10 (6.7)	1 (4.2)	12 (4.0)	11 (5.6)	2 (2.9)
Region, n (%)						
EU	98 (55.4)	76 (51.0)	9 (37.5)	124 (41.3)	90 (46.2)	20 (29.4)
US	42 (23.7)	39 (26.2)	14 (58.3)	77 (25.7)	56 (28.7)	35 (51.5)

Table 2: Baseline Demographics and Disease Characteristics by Study Cohorts (Pooled Safety Analysis Set)

Analysis Parameter	Cohort 2 [a] (N = 350)			Cohort 1 [a] (N = 563)		
	NexoBrid (N = 177)	Standard of Care (N = 149)	Gel Vehicle (N = 24)	NexoBrid (N = 300)	Standard of Care (N = 195)	Gel Vehicle (N = 68)
Other	37 (20.9)	34 (22.8)	1 (4.2)	99 (33.0)	49 (25.1)	13 (19.1)
Aetiology, n (%)						
Fire/Flame	111 (62.7)	96 (64.4)	20 (83.3)	205 (68.3)	131 (67.2)	54 (79.4)
Scald	51 (28.8)	39 (26.2)	2 (8.3)	70 (23.3)	44 (22.6)	6 (8.8)
Contact	14 (7.9)	13 (8.7)	2 (8.3)	23 (7.7)	19 (9.7)	8 (11.8)
Other	1 (0.6)	1 (0.7)	0	2 (0.7)	1 (0.5)	0
Number of Target Wounds, n (%)						
1	68 (38.4)	60 (40.3)	13 (54.2)	151 (50.3)	104 (53.3)	56 (82.4)
2	61 (34.5)	53 (35.6)	5 (20.8)	79 (26.3)	55 (28.2)	6 (8.8)
≥ 3	48 (27.1)	36 (24.2)	6 (25.0)	70 (23.3)	36 (18.5)	6 (8.8)
Number of Target Wounds						
Mean (SD)	2.0 (1.09)	1.9 (0.98)	1.7 (0.86)	1.9 (1.10)	1.7 (0.94)	1.3 (0.61)
Median	2.0	2.0	1.0	1.0	1.0	1.0
Min, Max	1, 7	1, 6	1, 3	1, 7	1, 6	1, 3
%TBSA (All Wounds)						
Mean (SD)	12.0 (6.05)	11.5 (6.39)	8.8 (3.65)	12.8 (7.08)	11.5 (6.47)	11.6 (7.37)
Median	11.0	10.0	8.3	11.8	9.5	9.8
Min, Max	3, 29	3, 30	3, 18	1, 39	3, 30	1, 28
%TBSA (Target Wounds)						
Mean (SD)	9.2 (5.07)	8.7 (5.11)	6.4 (3.60)	8.6 (5.48)	8.0 (4.89)	5.9 (3.45)

Table 2: Baseline Demographics and Disease Characteristics by Study Cohorts (Pooled Safety Analysis Set)

Analysis Parameter	Cohort 2 [a] (N = 350)			Cohort 1 [a] (N = 563)		
	NexoBrid (N = 177)	Standard of Care (N = 149)	Gel Vehicle (N = 24)	NexoBrid (N = 300)	Standard of Care (N = 195)	Gel Vehicle (N = 68)
Median	8.0	7.5	6.3	7.0	7.0	5.3
Min, Max	1, 25	2, 27	2, 18	1, 34	1, 27	1, 18
%DPT Area						
Mean (SD)	5.7 (3.73)	4.9 (3.31)	3.6 (1.99)	5.5 (4.34)	4.5 (3.31)	3.2 (2.55)
Median	5.0	4.5	4.0	4.5	4.0	3.0
Min, Max	0, 18	0, 24	0, 7	0, 26	0, 24	0, 11
%SPT Area						
Mean (SD)	1.4 (2.08)	1.7 (2.67)	1.3 (1.88)	1.4 (2.33)	1.6 (2.49)	1.1 (1.93)
Median	0.5	0	0.1	0	0	0
Min, Max	0, 15	0, 13	0, 7	0, 15	0, 13	0, 8
%FT Area						
Mean (SD)	2.1 (3.25)	2.1 (3.74)	1.5 (2.06)	1.7 (2.90)	1.9 (3.38)	1.7 (2.51)
Median	1.0	1.0	0.8	0	1.0	1.0
Min, Max	0, 20	0, 27	0, 8	0, 20	0, 27	0, 15

Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03
Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
DPT = deep partial thickness (second degree); EU = European Union; FT = full-thickness (third degree); ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; n = number of patients; N = total number of patients; SD = standard deviation; SPT = superficial partial thickness (second degree); TBSA = total burn surface area; US = United States
[a] Cohort 2 study MW2004-11-02 and Cohort 1 study MW2008-09-03 included both adult and paediatric subjects.
Source: ISS, Tables 14.1.2.2, 14.1.3.2, 14.1.2.1a, 14.1.3.1a, and 14.1.2.3

Table 3: Cumulative Patient Exposure to Study Drug and Follow-up Duration in Paediatric Population (Pivotal Study MW2012-01-01 [CIDS])

Analysis Parameter	NexoBrid (N = 69)	Standard of Care (N = 70)
Dose (g)		
n	66	0
Mean (SD)	5.108 (5.4315)	-
Median	3.409	-
Min, Max	0.62, 26.80	-
Duration in PY		
Total PY	75.11	75.40
1 application	74.01	-
2 applications	1.01	-
Duration (Months)		
n	69	69
Mean (SD)	13.078 (2.1010)	13.129 (2.3049)
Median	13.257	13.322
Min, Max	1.91, 17.57	0.76, 17.96

CSR = clinical study report; Max = maximum; Min = minimum; PY = person-years; SD = standard deviation.
Source: CIDS CSR, Tables 14.1.4.2 and 14.1.4.3

Table 4: Baseline Demographics and Disease Characteristics in Paediatric Population (Pivotal Study MW2012-01-01 [CIDS])

Analysis Parameter	NexoBrid (N = 69)	Standard of Care (N = 70)
Age (Years)		
Mean (SD)	5.89 (4.860)	5.75 (4.959)
Median	3.79	3.47
Min, Max	0.6, 18.6	0.7, 16.7
Age Group, n (%)		
0 to 23 months	20 (29.0)	22 (31.4)
24 months to 3 years	15 (21.7)	15 (21.4)
4 to 11 years	25 (36.2)	22 (31.4)
12 to < 18 years	9 (13.0)	11 (15.7)
Gender, n (%)		
Female	28 (40.6)	22 (31.4)
Male	41 (59.4)	48 (68.6)
Race, n (%)		
Asian	17 (24.6)	16 (22.9)
Black or African American	3 (4.3)	2 (2.9)
White	48 (69.6)	48 (68.6)
Other	1 (1.4)	4 (5.7)
Ethnicity, n (%)		
Hispanic or Latino	3 (4.3)	7 (10.0)
Not Hispanic or Latino	66 (95.7)	63 (90.0)
Region, n (%)		
Europe	42 (60.9)	39 (55.7)
US	12 (17.4)	16 (22.9)
Other	15 (21.7)	15 (21.4)
Aetiology, n (%)		
Fire/Flame	18 (26.1)	18 (25.7)
Scald	47 (68.1)	47 (67.1)
Contact	4 (5.8)	4 (5.7)
Multiple	0	1 (1.4)
Number of Target Wounds, n (%)		
1	49 (71.0)	56 (80.0)
2	16 (23.2)	11 (15.7)
3 to 4	4 (5.8)	2 (2.9)
≥ 5	0	1 (1.4)

Table 4: Baseline Demographics and Disease Characteristics in Paediatric Population (Pivotal Study MW2012-01-01 [CIDS])

Analysis Parameter	NexoBrid (N = 69)	Standard of Care (N = 70)
Number of Target Wounds		
Mean (SD)	1.36 (0.641)	1.27 (0.658)
Median	1.00	1.00
Min, Max	1.0, 4.0	1.0, 5.0
%TBSA (All Wounds)		
Mean (SD)	7.12 (4.942)	6.21 (4.872)
Median	6.00	4.65
Min, Max	1.3, 23.5	1.0, 29.1
%TBSA (Target Wounds)		
Mean (SD)	5.97 (4.477)	5.26 (4.325)
Median	4.50	4.00
Min, Max	1.0, 23.5	1.0, 23.0
%DPT Area		
Mean (SD)	4.03 (3.920)	3.45 (3.687)
Median	2.40	2.50
Min, Max	0.0, 23.5	0.0, 23.0
%SPT Area		
Mean (SD)	1.23 (1.659)	1.22 (2.279)
Median	0.50	0.00
Min, Max	0.0, 7.3	0.0, 10.0
%FT Area		
Mean (SD)	0.72 (2.004)	0.58 (1.440)
Median	0.00	0.00
Min, Max	0.0, 11.0	0.0, 9.0

CSR = clinical study report; DPT = deep partial thickness (second degree); FT = full-thickness (third degree); Max = maximum; Min = minimum; n = number of patients; N = total number of patients; SD = standard deviation; SPT = superficial partial thickness (second degree); TBSA = total burn surface area; US = United States

Source: CIDS CSR, Table 14.1.2a

Table 5: Cumulative Patient Exposure to Study Drug and Follow-up Duration (Paediatric Pooled Population)

Analysis Parameter	NexoBrid (N = 89)	Standard of Care (N = 86)
Dose (g)		
n	70	0
Mean (SD)	5.6 (5.39)	-
Median	3.7	-
Min, Max	1, 27	-
Duration in PY		
Total PY	30.95	29.89
1 application	29.66	-
2 applications	1.29	-
Duration (Months)		
n	89	86
Mean (SD)	4.2 (0.98)	4.2 (1.01)
Median	4.2	4.2
Min, Max	1, 7	1, 6

Notes: Data from paediatric subjects only in Studies MW2012-01-01 (CIDS), MW2008-09-03, and MW2004-11-02.
ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; PY = person-years; SD = standard deviation.
Source: ISS, Table 14.1.3.3.1.1

Table 6: Baseline Demographics and Disease Characteristics in Paediatric Population (Paediatric Pooled Population)

Analysis Parameter	NexoBrid (N = 89)	Standard of Care (N = 86)
Age (Years)		
Mean (SD)	7.0 (5.15)	6.7 (5.28)
Median	5.9	5.0
Min, Max	1, 19	1, 18
Age Group, n (%)		
0 to 23 months	20 (22.5)	22 (25.6)
24 months to 3 years	15 (16.9)	15 (17.4)
4 to 11 years	37 (41.6)	31 (36.0)
12 to < 18 years	17 (19.1)	18 (20.9)
Gender, n (%)		
Female	35 (39.3)	24 (27.9)
Male	54 (60.7)	62 (72.1)
Race, n (%)		
Asian	17 (19.1)	17 (19.8)
Black or African American	4 (4.5)	3 (3.5)
White	65 (73.0)	60 (69.8)
Other	3 (3.4)	6 (7.0)
Region, n (%)		
Europe	39 (43.8)	41 (47.7)
US	12 (13.5)	16 (18.6)
Other	38 (42.7)	29 (33.7)
Aetiology, n (%)		
Fire/Flame	28 (31.5)	28 (32.6)
Scald	56 (62.9)	53 (61.6)
Contact	5 (5.6)	4 (4.7)
Multiple	0	1 (1.2)
Number of Target Wounds, n (%)		
1	53 (59.6)	58 (67.4)
2	27 (30.3)	17 (19.8)
≥ 3	9 (10.1)	11 (12.8)
Number of Target Wounds		
Mean (SD)	1.5 (0.74)	1.5 (0.88)
Median	1.0	1.0
Min, Max	1, 4	1, 5

Table 6: Baseline Demographics and Disease Characteristics in Paediatric Population (Paediatric Pooled Population)

Analysis Parameter	NexoBrid (N = 89)	Standard of Care (N = 86)
%TBSA (All Wounds)		
Mean (SD)	8.4 (5.46)	7.8 (6.20)
Median	7.3	5.8
Min, Max	1, 24	1, 29
%TBSA (Target Wounds)		
Mean (SD)	7.2 (4.83)	6.6 (5.44)
Median	6.0	5.0
Min, Max	1, 24	1, 26
%DPT Area		
Mean (SD)	4.9 (4.25)	3.9 (4.22)
Median	3.6	3.0
Min, Max	0, 24	0, 24
%SPT Area		
Mean (SD)	1.4 (1.81)	1.4 (2.54)
Median	0.5	0.0
Min, Max	0, 7	0, 10
%FT Area		
Mean (SD)	0.9 (2.26)	1.3 (3.03)
Median	0.0	0.0
Min, Max	0, 11	0, 19

DPT = deep partial thickness (second degree); FT = full-thickness (third degree); Max = maximum; ISS = Integrated Summary of Safety; Min = minimum; n = number of patients; N = total number of patients; SD = standard deviation; SPT = superficial partial thickness (second degree); TBSA = total burn surface area; US = United States.
Source: ISS, Tables 14.1.2.1 and 14.1.2.1.1

Table 7: Cumulative Patient Exposure to Study Drug and Follow-up Duration (Adult Pooled Population)

Analysis Parameter	NexoBrid (N = 280)	Standard of Care (N = 179)	Placebo (N=68)
Dose (g)			
n	274	0	65
Mean (SD)	15.7 (10.84)	-	156.7 (144.67)
Median	12.0	-	100.0
Min, Max	2, 60	-	20, 720
Duration in PY			
Total PY	84.36	57.01	20.57
1 application	70.37	-	-
2 applications	14	-	-
Duration (Months)			
n	280	179	68
Mean (SD)	3.6 (1.93)	3.8 (1.65)	3.6 (1.43)
Median	3.9	3.9	3.9
Min, Max	0, 15	0, 13	0, 7

Notes: Data from adult subjects only in Studies MW2001-10-03, MW2002-04-01, MW2005-10-05, MW2008-09-03, MW2004-11-02, and MW2010-03-02 (DETECT).
ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; PY = person-years; SD = standard deviation.
Source: ISS, Table 14.1.3.3.1.1

Table 8: Baseline Demographics and Disease Characteristics in Adult Population Only (Adult Pooled Population)

Analysis Parameter (Statistics [a])	NexoBrid (N = 280)	Standard of Care (N = 179)	Placebo (N = 68)
Age (Years)			
Mean (SD)	38.2 (13.98)	37.5 (13.64)	37.8 (13.56)
Median	37.1	35.3	36.2
Min, Max	18, 76	18, 73	18, 70
Age Group, n (%)			
< 18 years	0	0	0
18 to 64 years	269 (96.1)	174 (97.2)	64 (94.1)
≥ 65 years	11 (3.9)	5 (2.8)	4 (5.9)
Gender, n (%)			
Female	73 (26.1)	44 (24.6)	21 (30.9)
Male	207 (73.9)	135 (75.4)	47 (69.1)
Race, n (%)			
Asian	38 (13.6)	19 (10.6)	12 (17.6)
Black or African American	22 (7.9)	21 (11.7)	12 (17.6)
White	10 (3.6)	9 (5.0)	42 (61.8)
Other	210 (75.0)	130 (72.6)	2 (2.9)
Region, n (%)			
Europe	117 (41.8)	80 (44.7)	20 (29.4)
US	77 (27.5)	56 (31.3)	35 (51.5)
Other	86 (30.7)	43 (24.0)	13 (19.1)
Aetiology, n (%)			
Fire/Flame	195 (69.6)	121 (67.6)	54 (79.4)
Scald	61 (21.8)	38 (21.2)	6 (8.8)
Contact	22 (7.9)	19 (10.6)	8 (11.8)
Multiple	2 (0.7)	1 (0.6)	0
Number of Target Wounds, n (%)			
1	147 (52.5)	102 (57.0)	56 (82.4)
2	68 (24.3)	49 (27.4)	6 (8.8)
≥ 3	65 (23.2)	28 (15.6)	6 (8.8)

Table 8: Baseline Demographics and Disease Characteristics in Adult Population Only (Adult Pooled Population)

Analysis Parameter (Statistics [a])	NexoBrid (N = 280)	Standard of Care (N = 179)	Placebo (N = 68)
Number of Target Wounds			
Mean (SD)	1.8 (1.12)	1.6 (0.90)	1.3 (0.61)
Median	1.0	1.0	1.0
Min, Max	1, 7	1, 6	1, 3
%TBSA (All Wounds)			
Mean (SD)	12.8 (7.22)	11.2 (6.38)	11.6 (7.37)
Median	11.0	9.3	9.8
Min, Max	1, 39	3, 30	1, 28
%TBSA (Target Wounds)			
Mean (SD)	8.4 (5.55)	7.6 (4.60)	5.9 (3.45)
Median	7.0	6.3	5.3
Min, Max	1, 34	1, 27	1, 18
%DPT Area			
Mean (SD)	5.3 (4.31)	4.4 (2.99)	3.2 (2.55)
Median	4.0	4.0	3.0
Min, Max	0, 26	0, 15	0, 11
%SPT Area			
Mean (SD)	1.4 (2.34)	1.5 (2.39)	1.1 (1.93)
Median	0.0	0.0	0.0
Min, Max	0, 15	0, 13	0, 8
%FT Area			
Mean (SD)	1.7 (2.90)	1.6 (3.05)	1.7 (2.51)
Median	0.0	1.0	1.0
Min, Max	0, 20	0, 27	0, 15

DPT = deep partial thickness (second degree); FT = full-thickness (third degree); ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; n = number of patients; N = total number of patients; SD = standard deviation; SPT = superficial partial thickness (second degree); TBSA = total burn surface area; US = United States

[a] The percentages are based on the number of patients in the analysis cohort.

Per patient is calculated as sum of the analysis parameter value of all patient's target wounds.

Source: ISS, Table 14.1.2.1.1

Table 9: Cumulative Patient Exposure to Study Drug and Follow-up Duration in Total Pooled Population (Adult and Paediatric Pooled Population)

Analysis Parameter	NexoBrid (N = 369)	Standard of Care (N = 265)	Placebo (N=68)
Dose (g)			
n	344	0	65
Mean (SD)	13.7 (10.83)	-	156.7 (144.67)
Median	10.0	-	100.0
Min, Max	1, 60	-	20, 720
Duration in PY			
Total PY	115.31	86.9	20.57
1 application	100.2	-	-
2 applications	15.29	-	-
Duration (Months)			
n	369	265	68
Mean (SD)	3.8 (1.77)	3.9 (1.48)	3.6 (1.43)
Median	3.9	3.9	3.9
Min, Max	0, 15	0, 13	0, 7

Notes: Data from adult and paediatric subjects in Studies MW2012-01-01 (CIDS), MW2001-10-03, MW2002-04-01, MW2005-10-05, MW2008-09-03, MW2004-11-02, and MW2010-03-02 (DETECT).
ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; PY = person-years; SD = standard deviation.
Source: ISS, Table 14.1.3.3.1

Table 10: Baseline Demographics and Disease Characteristics in Total Pooled Population (Adult and Paediatric Pooled Population)

Analysis Parameter	NexoBrid (N = 369)	Standard of Care (N = 265)	Placebo (N = 68)
Age (Years)			
Mean (SD)	30.7 (18.25)	27.5 (18.54)	37.8 (13.56)
Median	29.7	25.5	36.2
Min, Max	1, 76	1, 73	18, 70
Age Group, n (%)			
0 to 23 months	20 (5.4)	22 (8.3)	0
24 months to 3 years	15 (4.1)	15 (5.7)	0
4 to 11 years	37 (10.0)	31 (11.7)	0
12 to < 18 years	17 (4.6)	18 (6.8)	0
18 to 64 years	269 (72.9)	174 (65.7)	64 (94.1)
≥ 65 years	11 (3.0)	5 (1.9)	4 (5.9)
Gender, n (%)			
Female	108 (29.3)	68 (25.7)	21 (30.9)
Male	261 (70.7)	197 (74.3)	47 (69.1)
Race, n (%)			
Asian	55 (14.9)	36 (13.6)	12 (17.6)
Black or African American	26 (7.0)	24 (9.1)	12 (17.6)
Caucasian	275 (74.5)	190 (71.7)	42 (61.8)
Other	13 (3.5)	15 (5.7)	2 (2.9)
Region, n (%)			
Europe	156 (42.3)	121 (45.7)	20 (29.4)
US	89 (24.1)	72 (27.2)	35 (51.5)
Other	124 (33.6)	72 (27.2)	13 (19.1)
Aetiology, n (%)			
Fire/Flame	223 (60.4)	149 (56.2)	54 (79.4)
Scald	117 (31.7)	91 (34.3)	6 (8.8)
Contact	27 (7.3)	23 (8.7)	8 (11.8)
Multiple	0	1 (0.4)	0
Other	2 (0.5)	1 (0.4)	0
Number of Target Wounds, n (%)			
1	200 (54.2)	160 (60.4)	56 (82.4)
2	95 (25.7)	66 (24.9)	6 (8.8)
≥ 3	74 (20.1)	39 (14.7)	6 (8.8)

Table 10: Baseline Demographics and Disease Characteristics in Total Pooled Population (Adult and Paediatric Pooled Population)

Analysis Parameter	NexoBrid (N = 369)	Standard of Care (N = 265)	Placebo (N = 68)
Number of Target Wounds			
Mean (SD)	1.8 (1.05)	1.6 (0.90)	1.3 (0.61)
Median	1.0	1.0	1.0
Min, Max	1, 7	1, 6	1, 3
%TBSA (All Wounds)			
Mean (SD)	11.7 (7.08)	10.1 (6.51)	11.6 (7.37)
Median	10.0	8.5	9.8
Min, Max	1, 39	1, 30	1, 28

DPT = deep partial thickness (second degree); FT = full-thickness (third degree); ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; n = number of patients; N = total number of patients; SD = standard deviation; SPT = superficial partial thickness (second degree); TBSA = total burn surface area
Source: ISS, Table 14.1.2.1

PART II: Module SIV - Populations not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

The following significant exclusion criteria are based on the criteria from the phase III studies MW2010-03-02 (DETECT), MW2004-11-02, and MW2012-01-01 (CIDS).

Treatment of facial, perineal, or genital burns

– **Reason for exclusion:**

This criterion was implemented in the clinical development programme, based on the irritant potential of NexoBrid showed in the non-clinical studies and the delicate nature of skin in the facial, perineal, or genital areas.

– **Is it considered to be included as missing information?**

No

– **Rationale:**

The safety profile of NexoBrid is not expected to differ in patients with facial, perineal, or genital burns as shown by published cases of successful use (Schulz et al, 2017; Hirche et al, 2020) and such use in clinical practice is at the discretion of treating physician. However, NexoBrid must be used with caution in such patients.

The European consensus guidelines on enzymatic debridement highly recommend enzymatic debridement with NexoBrid for facial burns (Hirche et al, 2020). Due to its unique anatomy in line with high demands on preservation of dermis due to the functional and aesthetic benefits, enzymatic debridement shows its strengths of selective eschar removal in the face. However, application of NexoBrid requires significant experience with enzymatic debridement and as such, this region should not be chosen by those only beginning their enzymatic debridement treatment experience (Hirche et al, 2020).

The European consensus guidelines on enzymatic debridement recommend enzymatic debridement for perineal and genital burns (Hirche et al, 2020) since enzymatic debridement in these areas may allow earlier and more selective debridement, promoting spontaneous healing and potentially leading to improved outcomes (Schulz et al, 2018).

Pregnant or lactating women

– **Reason for exclusion:**

Pregnant or breastfeeding women were excluded from the clinical development according to standard ethical reasons.

– **Is it considered to be included as missing information?**

Yes

– **Rationale:**

Not applicable.

Selected cardiopulmonary disease

– **Reason for exclusion:**

This exclusion criterion was established in phase III studies to minimise potential confounding factors for evaluation of study findings and to minimise potential risks to this patient sub-population.

– **Is it considered to be included as missing information?**

No

– **Rationale:**

'Increased mortality in patients with cardiopulmonary disease' represented an important potential risk of NexoBrid in the initial EU RMP, based on 5 deaths encountered in the initial clinical development programme in the NexoBrid treatment group (as opposite to a single death that occurred in the SOC treatment group).

All 5 subjects treated with NexoBrid who died had significant pre-existing co-morbidities, including COPD, bronchopneumonia, infection, or smoke inhalation that developed into septicaemia, in addition to severe burns. These co-morbidities provided more plausible explanation for the cause of death than NexoBrid therapy as burn patients with a history of pulmonary circulation disorders or pulmonary disease are at increased risk of death as showed in a large US study, analysing the data from patients with acute burn injury (Thombs et al, 2007).

Neither the non-clinical and clinical development programme for NexoBrid nor the post-marketing experience to date suggest any role of NexoBrid in worsening of cardiopulmonary disease in burn patients and as such, this safety concern was removed from the safety profile of NexoBrid during EU RMP update.

The safety profile of NexoBrid is not expected to differ in this patient sub-population to general safety profile seen in the NexoBrid development programme.

Poorly controlled diabetes mellitus

– **Reason for exclusion:**

These exclusion criteria were established in phase III studies to minimise potential confounding factors for evaluation of study findings and to minimise potential risks to these patient sub-populations.

– **Is it considered to be included as missing information?**

No

– **Rationale:**

Diabetes mellitus is an important factor adversely affecting wound healing in general, including burn wounds. The safety profile of NexoBrid is not expected to differ in this patient sub-population to general safety profile seen in the NexoBrid development programme. However, caution must be exercised when treating burn wounds on diabetic foot, especially with diabetic foot wounds (Berner et al, 2018). The use of NexoBrid on diabetic foot burns is not recommended.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programme

The clinical development programme is unlikely to detect certain types of adverse reactions, such as rare adverse reactions or adverse reactions with a long latency.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 11: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Elderly patients (> 65 years of age)	Elderly patients were not excluded from the clinical development programme; however, only a limited number of patients above 65 years of age have been exposed to NexoBrid. Refer to Table 2 for exposure data in the elderly patients in the completed clinical trials in the pooled safety analysis set (Cohort 1 and Cohort 2 studies).
Patients with relevant comorbidities: – Patients with selected cardiopulmonary impairment (myocardial infarction within 6 months prior to injury, severe pulmonary hypertension, severe COPD, or pre-existing oxygen-dependent pulmonary diseases, severe bronchopneumonia within 1 month prior to injury, and steroid-dependent or uncontrolled asthma)	Not included in the clinical development programme.
– Immunocompromised patients	Not included in the clinical development programme.
– Patients with renal and/or hepatic impairment	Not included in the clinical development programme.
– Patients with a disease severity different from inclusion criteria in clinical trials o Patients with burn wounds > 30% TBSA o Patients with circumferential anterior/posterior trunk FT fire/flame burns > 15% TBSA (‘circumferential’ is defined as encircling ≥ 80% of the trunk circumference) o Circumferential DPT (>80% of the limb circumference) and/or FT burns defined as extremities at risk o Patients with pre-enrolment escharotomy (in prospective studies)	The primary intention of initial clinical development programme was to study the most homogenous population possible. No or limited data are available for the patients with a different disease severity as specified on the left.

COPD = chronic obstructive pulmonary disease; DPT = deep partial thickness; FT = full-thickness; TBSA = total body surface area

PART II: Module SV – Post-Authorisation Experience

NexoBrid was first approved via centralised procedure in the EU on 18 December 2012 for eschar removal in adults with deep partial thickness (DPT) and FT thermal burns. This date represents the International Birth Date (IBD) for NexoBrid.

NexoBrid is currently authorised in 40 countries [redacted].

NexoBrid is authorised for the same indication across all countries worldwide.

In addition, NexoBrid is available in Switzerland [redacted] per a special agreement and in Australia [redacted] per a special scheme, without a marketing authorisation in place and for the same indication as in the EU/EEA.

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Internal company sales data were used as a source for the calculation of patient exposure from the marketing experience.

SV.1.2 Exposure

Cumulatively since the IBD until 17 December 2021, an estimated 8,828 patients were exposed to NexoBrid worldwide, of which 7,368 in the EU/EEA and 1,460 in non-EU/EEA countries. In addition, 120 patients received NexoBrid in the US under the expanded access treatment protocol MW2018-06-21 (NEXT).

The cumulative exposure data are presented in Table 12 by region [redacted] where NexoBrid is marketed. The exact exposure data (number of applications, dose applied, percentage of TBSA treated) are currently not available for the post-marketing data sources.

Table 12: Cumulative Patient Exposure from the Post-Marketing Experience

Region [redacted]	Cumulative Patient Exposure
EU/EEA	**7,368**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 12: Cumulative Patient Exposure from the Post-Marketing Experience

Region/Country	Cumulative Patient Exposure
[redacted]	[redacted]
[redacted]	[redacted]
Non-EU/EEA	**1,460**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Total	**8,828**

EEA = European Economic Area; EU = European Union

[redacted]

PART II: Module SVI – Additional EU requirements for safety specification

Potential for misuse for illegal purposes

NexoBrid has no known potential for misuse for illegal purposes.

PART II: Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

None.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important Identified Risk 1: Pain

Potential Mechanism(s):

Enzymatic debridement is a painful procedure as pain accompanies both the product application and actual debris removal (Hirche et al, 2017; Hirche et al, 2020).

Evidence Source(s) and Strength of Evidence:

This risk is based on the findings from the non-clinical as well as clinical part of the development programme for NexoBrid, where local pain was identified as an accompanying symptom of enzymatic debridement.

Characterisation of the Risk:

Clinical Trials (Pooled Safety Analysis Set – Cohort 1 and Cohort 2 Studies; SIII.1)

'All treatment-emergent AEs (TEAEs)' were defined as those events that occurred in clinical studies after the start of treatment (NexoBrid, SOC, or placebo [gel vehicle]) and up to 3 months post wound closure of all treated wounds (i.e., acute phase) with the exception of Study MW2005-10-05, which was 1 month post wound closure.

Data from the 12- and 24-month follow-up in Study MW2010-03-02 (DETECT) are presented separately.

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Acute Phase (Up to 3 Months Post Wound Closure)

The incidence rates of pain-related treatment-emergent adverse events (TEAEs)[2] in NexoBrid treatment group by study cohort are summarised in Table 13.

[2] Preferred terms (PTs) for pain-related events were grouped by clinical inspection of the data and included (if reported as local target wound-related events): pain, procedural pain, application site pain, post traumatic pain, local target wound-related pain in extremity, and wound complication (referring to wound pain).

Table 13: Summary of TEAEs and NexoBrid-Related TEAEs of Pain in NexoBrid Treatment Group by Study Cohorts (Pooled Safety Analysis Set)

TEAE (MedDRA PT)	Cohort 2 NexoBrid (N = 177) n (%)		Cohort 1 NexoBrid (N = 300) n (%)	
	All TEAEs	Related	All TEAEs	Related
Application site pain	0	0	1 (0.3)	0
Pain	7 (4.0)	3 (1.7)	26 (8.7)	18 (6.0)
Pain in extremity	1 (0.6)	0	1 (0.3)	0
Procedural pain	0	0	1 (0.3)	0
Wound complication	1 (0.6) [a]	1 (0.6) [a]	1 (0.3) [a]	1 (0.3) [a]

Note: Subjects are counted only once in each MedDRA PT category.
Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03
Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
[a] Verbatim term of uncontrolled target wound-related pain.
Source: ISS, Tables 14.3.1.15.1a, 14.3.1.15.2, 14.3.1.5.1a, and 14.3.1.5.2

One patient (1/20; 5.0%) with pain in Table 13 was a paediatric patient treated in Cohort 1 studies (MW2004-11-02 and MW2008-09-03; refer to PART II: Module SIII) (N = 20).

Routine preventive analgesia and general pain management has only been implemented at the time of later clinical studies MW2005-10-05, MW2008-09-03, MW2004-11-02, and MW2010-03-02 (DETECT), which resulted in higher incidence rate of pain reported from the early clinical studies (MW2001-10-03 and MW2002-04-01), where analgesia was provided on-demand basis. Therefore, the incidence of pain-related events by pre- and post-implementation of preventive measures is presented in Table 14.

Table 14: Pain TEAEs in NexoBrid Treatment Group by Preferred Term and Pre- and Post-Implementation of Preventive Measures

Pain TEAE (MedDRA PT)	Pre-Implementation Pool [a]	Post-Implementation Pool [b]
	NexoBrid (N = 77) n (%)	NexoBrid (N = 223) n (%)
Any pain TEAE	18 (23.4)	9 (4.0)
Application site pain	1 (1.3)	0
Pain	18 (23.4)	8 (3.6)
Pain in extremity	0	1 (0.4)
Procedural pain	1 (1.3)	0
Wound complication	0	1 (0.4) [c]

Note: Subjects are counted only once in each MedDRA PT category.
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
[a] Studies MW2001-10-03 and MW2002-04-01.
[b] Studies MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02 (DETECT).
[c] Verbatim term of 'uncontrolled target wound-related pain'.
Source: ISS, Table 14.3.4.1.1a

There was a similar frequency of 'any pain TEAEs' in the NexoBrid (4.5%) and SOC (4.0%) treatment groups of Cohort 2 and there were 2 patients (8.3%) with pain-related events in the placebo group (Table 15).

In Cohort 1, there was a higher frequency of 'any pain TEAE'[2] in the NexoBrid and placebo group (9.0% and 8.8%, respectively) compared with the SOC group (4.1%) (Table 15), which is expected since Cohort 1 also includes studies from pre-implementation of preventive procedures for the use of NexoBrid.

Table 15: Summary of Any Pain-Related TEAE by Cohort and Treatment Group (Pooled Safety Analysis Set)

Pain TEAE (MedDRA PT)	NexoBrid n (%)	SOC n (%)	Placebo n (%)
Cohort 1			
N	300	195	68
Any pain TEAE	27 (9.0)	8 (4.1)	6 (8.8)
Pain	26 (8.7)	8 (4.1)	4 (5.9)
Application site pain	1 (0.3)	0	0
Pain in extremity	1 (0.3)	0	1 (1.5)
Procedural pain	1 (0.3)	0	0
Wound complication	1 (0.3) [a]	0	0
Post-traumatic pain	0	0	1 (1.5)
Cohort 2			
N	177	149	24
Any pain TEAE	8 (4.5)	6 (4.0)	2 (8.3)
Pain	7 (4.0)	6 (4.0)	0
Pain in extremity	1 (0.6)	0	1 (4.2)
Wound complication	1 (0.6) [a]	0	0
Post-traumatic pain	0	0	1 (4.2)

Note: Subjects are counted only once in each MedDRA PT category.
Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03
Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; SOC = standard of care; TEAE = treatment-emergent adverse event.
[a] Verbatim term of 'uncontrolled target wound-related pain'.
Source: ISS, Tables 14.3.1.15.1a and 14.3.1.15.2

By MedDRA PT, the frequencies of pain, target wound-related pain in extremity, wound complication (verbatim term of target wound-related uncontrolled pain), and post-traumatic pain were similar in the NexoBrid and SOC treatment groups in Cohort 2. In Cohort 1, the frequencies of pain in extremity, procedural pain, wound complication, and post-traumatic pain were similar across treatment groups (Table 15).

One patient (0.3%) in the Cohort 1 in NexoBrid treatment group had serious event of paint in extremity. No serious pain-related events were reported in the Cohort 2 in NexoBrid treatment group.

The majority of reported events in NexoBrid treatment group were mild to moderate in severity. Three patients (1.7%) in Cohort 2 and 11 patients (3.7%) in Cohort 1 had a severe TEAE of pain. None of severe events were related to NexoBrid.

All patients in Cohort 2 experienced pain (by MedDRA PT) during treatment or during the first week after treatment. Pain in extremity and wound complication (verbatim term of target wound-related uncontrolled pain) were experienced by 1 patient each (both in the NexoBrid treatment group of Cohort 2) during week 2 to week 4 after treatment. In Cohort 1, one patient in the NexoBrid group experienced pain more than 8 weeks after treatment.

The data from study MW2010-03-02 (DETECT) showed that the use of general anaesthesia was much higher for patients treated with the SOC, related to surgical eschar removal, than for patients treated with NexoBrid after first application (42 patients [87.50%] patients treated with the SOC compared with 4 patients [5.19%] treated with NexoBrid, respectively).

12 Months and 24 Months Post Wound Closure (Study MW2010-03-02 [DETECT] Follow-Up Data)

Only a single patient (1.3%) in the NexoBrid treatment group reported an event of pain during the time period from 3 to 12 months post wound closure, assessed as non-serious and unrelated to NexoBrid.

No patient had a pain event in the time period from 12 to 24 months post wound closure.

Clinical Trials (Paediatric Population; SIII.2)

TEAEs were defined as adverse events that occurred after the start of treatment and up to 3 months post wound closure (i.e., acute phase). Additionally, the follow-up data for Study MW2012-01-01 (CIDS) are shown for the period from 12 weeks to 12 months post would closure.

Data are presented in this sub-section for the Study MW2012-01-01 (CIDS) and pooled populations (paediatric and adult) from the pooled studies (refer to SIII.2).

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Study MW2012-01-01 (CIDS): Acute Phase (Up to 12 Weeks Post Wound Closure)

The incidence rates of pain-related TEAEs[3] by treatment group are summarised in Table 16.

Table 16: Summary of Pain TEAEs in Pivotal Study MW2012-01-01 (CIDS) by Treatment Group (0 to 12-Week Follow-Up Period)

TEAE (MedDRA PT)	NexoBrid (N = 69) n (%)	SOC (N = 70) n (%)
Any pain TEAE	3 (4.3)	3 (4.3)
Pain	1 (1.4)	2 (2.9)

[3] PTs for pain-related events were grouped by clinical inspection of the data and included (if reported as local target wound-related events): pain, procedural pain, application site pain, post traumatic pain, local target wound-related pain in extremity, and wound complication (referring to wound pain).

Table 16: Summary of Pain TEAEs in Pivotal Study MW2012-01-01 (CIDS) by Treatment Group (0 to 12-Week Follow-Up Period)

TEAE (MedDRA PT)	NexoBrid (N = 69) n (%)	SOC (N = 70) n (%)
Pain in extremity	0	1 (1.4)
Wound complication	2 (2.9) [a]	0

Note: Subjects are counted only once in each MedDRA PT category.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; SOC = standard of care; TEAE = treatment-emergent adverse event
[a] Verbatim terms of 'wound pain' and 'wound pain (during movement)'.
Source: CIDS CSR, Table 14.3.1.1.2.7

None of these events were assessed as serious. All events were mild or moderate in severity. Only 2 events were considered as related to NexoBrid.

The incidence of 'any pain TEAE' was 4.3% in the NexoBrid and SOC treatment groups of this study (Table 16).

No statistically significant differences in the Face-Pain Scale-Revised (FPS-R) Scale scores for patients above 4 years of age (Hicks et al, 2001) were observed in either age group at screening between the NexoBrid and SOC treatment groups.

The FPS-R Scale scores in the NexoBrid and SOC treatment groups on Day 1 until Day 7 post eschar removal were not statistically different in either age group with the exception of FPS-R Scale scores on Day 5 and Day 6 post eschar removal among patients above 4 years of age (p-value <0.05).

Overall, no patients treated with NexoBrid in either age group experienced a shift from a normal baseline level to a clinically significant abnormal pain assessment post treatment.

Study MW2012-01-01 (CIDS): 12 Weeks to 12 Months Post Wound Closure Follow-Up Data

No pain-related TEAE was reported in the period from 12 weeks to 12 months post wound closure.

Pooled Populations (Paediatric and Adult)

The incidence rates of 'any pain TEAE'[3] in the paediatric and adult pooled populations post-implementation of corrective procedures by treatment group 12 weeks post wound closure are provided in Table 17.

Table 17: Summary of Pain TEAEs in Adult and Paediatric Pooled Populations (Post-Implementation of Corrective Procedures) by Treatment Group (12 Weeks Post Wound Closure)

TEAE (MedDRA PT)	Paediatric Pooled Population [a]		Adult Pooled Population [b]		
	NexoBrid (N = 89) n (%)	SOC (N = 86) n (%)	NexoBrid (N = 203) n (%)	SOC (N = 144) n (%)	Placebo (N = 33) n (%)
Any pain TEAE	7 (7.9)	8 (9.3)	8 (3.9)	5 (3.5)	2 (6.1)
Pain	5 (5.6)	6 (7.0)	7 (3.4)	5 (3.5)	0
Wound complication	2 (2.2) [c]	0	1 (0.5) [d]	0	0

Table 17: Summary of Pain TEAEs in Adult and Paediatric Pooled Populations (Post-Implementation of Corrective Procedures) by Treatment Group (12 Weeks Post Wound Closure)

TEAE (MedDRA PT)	Paediatric Pooled Population [a]		Adult Pooled Population [b]		
	NexoBrid (N = 89) n (%)	SOC (N = 86) n (%)	NexoBrid (N = 203) n (%)	SOC (N = 144) n (%)	Placebo (N = 33) n (%)
Pain in extremity	0	1 (1.2)	1 (0.5)	0	1 (3.0)
Procedural pain	0	1 (1.2)	0	0	0
Post-traumatic pain	0	0	0	0	1 (3.0)

Note: Subjects are counted only once in each MedDRA PT category.
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
[a] Studies MW2012-01-01 [CIDS], MW2008-09-03, and MW2004-11-02 (paediatric patients only)
[b] Studies MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02 (adult patients only)
[c] Verbatim terms of 'wound pain' and 'wound pain (during movement)'.
[d] Verbatim term of 'uncontrolled target wound-related pain'.
Source: ISS, Table 14.3.1.7.1.1

There was no significant difference in the incidence of 'any pain TEAE' between the adult pooled population post-implementation of corrective procedures and the paediatric population in study MW2012-01-01 (CIDS) (3.9% and 4.3%, respectively; Table 17 and Table 16).

Although the incidence of 'any pain TEAE' in the NexoBrid group in the pooled paediatric population was higher in comparison to the incidence seen in NexoBrid group in the adult pooled population (7.9% versus 3.9%) (Table 17), the incidence was similar between the NexoBrid and the SOC groups in the paediatric population (7.9% and 9.3%, respectively) (Table 17).

There were no noteworthy trends in distribution of pain TEAEs across the age groups in the paediatric pooled population. The number of paediatric patients with pain TEAE was low across all age groups in either treatment arm.

No patient in the paediatric pooled population and one patient in the adult pooled population had event assessed as serious.

Impact on Quality of Life

Pain, especially in its severe form, may significantly reduce the quality of patient's life during the burn trauma treatment.

Patients reported significant pain during and after enzymatic debridement. Therefore, adequate analgesia is essential (Hirche et al, 2020). Underestimation of enzymatic debridement invasiveness may lead to inappropriate anaesthesia and even for the need for rescue analgesia (Galeiras et al, 2018).

Post-Marketing Experience

Evaluation of data collected from the post-marketing experience (spontaneous and solicited sources of information) did not identify any new and significant information relevant to this risk and these data are in line with the safety profile of NexoBrid from the development programme.

Cumulatively since the IBD until 17 December 2021[4], 39 adverse drug reactions (ADRs) of pain were reported from spontaneous post-marketing sources in valid individual case safety reports. This represents a reporting rate of 0.44%, considering the total post-marketing patient exposure of 8,828 patients (refer to Section SV.1.2).

Of the patients analysed in the retrospective, non-interventional post-authorisation safety study (PASS) MW2013-06-01 (NexoPASS) completed in 2019 (N = 164), only 1 patient (0.6%) reported pain[5] during the NexoBrid treatment (described as patient's repeated complaints, followed by prescription of pain medication). Study results showed high compliance rates with the required pain management before NexoBrid administration (93.9%) and before NexoBrid removal from the target wound (79.2%).

According to worst-case analysis[6], 29 patients (17.7%) suffered from pain during NexoBrid application (in 28 patients [17.1%] assessed as related to NexoBrid).

Two events of pain in 2 patients (1.2%) were assessed as related to NexoBrid (but not meeting the study definition of pain) were serious and both resolved.

The majority of events reported within the first 72 hours described post NexoBrid treatment-related pain and not the procedural pain during debridement with NexoBrid.

Risk Factors and Risk Groups:

No risk groups or specific risk factors have been identified for the events of pain associated with NexoBrid enzymatic debridement.

Preventability:

Enzymatic debridement, including removal of NexoBrid after debridement, is a painful procedure and requires adequate analgesia and/or 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.

Refer to Part V.2 for a detailed description of the additional risk minimisation measures in place, designed to further mitigate the risk of pain in burn patients treated with NexoBrid.

Impact on the Risk-Benefit Balance of the Product:

Pain associated with debridement of eschars has a significant impact on burn patients and wound healing process and as such, pain associated with NexoBrid therapy represents an important identified risk. The highly effective risk minimisation measures in place markedly decreased the occurrence of debridement-related pain to minimum, making the overall impact of this risk on the product acceptable in the light of the anticipated benefits to burn patients.

[4] The date represents the data lock point for the Addendum to Clinical Overview submitted for the second renewal of the marketing authorisation for NexoBrid, providing the most up-to-date post-marketing data for NexoBrid.

[5] Pain was defined as 'at least 2 pain events during the debridement procedure, from start of treatment until end of soaking period, 2 hours post-NexoBrid removal with subsequent pain medication.'

[6] Sensitivity analyses were conducted to assess robustness of the study results, i.e., best-case analyses with subjects treated in compliance with the educational materials and worst-case analyses, based on an incidence rate for which each 'possible' adverse event of interest is regarded as a definite adverse event of interest.

Public Health Impact:

It is anticipated that ≥1 in 100 to <1 in 10 patients treated with NexoBrid in the post-marketing setting will experience local pain.

Considering the low overall incidence of deep burn injuries and the eligibility criteria to NexoBrid treatment, the public health impact of this risk occurring in association with NexoBrid therapy is considered low.

SVII.3.1.2 Important Identified Risk 2: Pyrexia/Hyperthermia

Potential Mechanism(s):

Not yet fully established specifically for NexoBrid.

Pyrexia is a well-known phenomenon in burn patients as virtually all burn patients have elevated core body temperature (Mavrogordato et al, 2009; Bayuo, 2017). The burn patient is catabolic (Williams et al, 2009; Williams and Herndon, 2017) with a very high basal metabolic rate, often accompanied with elevated body temperature. However, the exact mechanism has not been fully understood (Mavrogordato et al, 2009).

Mild hyperthermia within the first 24 hours post injury is almost always the result of pyrogen release. After 72 hours, burn patients develop systemic inflammatory response syndrome, characterised by tachycardia, relative hypotension, and hyperthermia (Jeschke et al, 2007; Bayuo, 2017).

The inflammatory reactions involved in the wound-healing process, as well as wound contamination, may contribute to this phenomenon in burn patients. In addition, occlusive dressings that do not allow heat dissipation may be a source of pyrexia (D'Avignon and Murray; Hirche et al, 2017).

Evidence Source(s) and Strength of Evidence:

Pyrexia/hyperthermia were the most commonly reported adverse reactions associated with the use of NexoBrid in clinical trials.

The frequency of the pyrexia/hyperthermia decreased when NexoBrid was used in a regimen, introducing antibacterial soaking of the treatment area before and after NexoBrid application and administration of preventive analgesia.

Characterisation of the Risk:

<u>Clinical Trials</u> (Pooled Safety Analysis Set - Cohort 1 and Cohort 2 Studies; SIII.1)

'All TEAEs' were defined as those events that occurred in clinical studies after the start of treatment (NexoBrid, SOC, or placebo [gel vehicle]) and up to 3 months post wound closure of all treated wounds (i.e., acute phase) with the exception of Study MW2005-10-05, which was 1 month post wound closure.

Data from the 12- and 24-month follow-up in Study MW2010-03-02 (DETECT) are presented separately.

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Acute Phase (Up to 3 Months Post Wound Closure)

The incidence rates of pyrexia/hyperthermia-related TEAEs[7] in NexoBrid treatment group by study cohort are summarised in Table 18.

Table 18: Summary of TEAEs and NexoBrid-Related TEAEs of Pyrexia/Hyperthermia in NexoBrid Treatment Group by Study Cohorts (Pooled Safety Analysis Set)

TEAE (MedDRA PT)	Cohort 2 (N = 177) n (%)		Cohort 1 (N = 300) n (%)	
	All TEAEs	Related	All TEAEs	Related
Body temperature increased	1 (0.6)	1 (0.6)	2 (0.7)	1 (0.3)
Hyperthermia	5 (2.8)	0	5 (1.7)	0
Pyrexia	21 (11.9)	4 (2.3)	54 (18.0)	6 (2.0)

Note: Subjects are counted only once in each MedDRA PT category.
Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03
Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
Source: ISS, Tables 14.3.1.14.1a, 14.3.1.14.2, 14.3.1.5.1a, and 14.3.1.5.2

Four patients (4/20; 20.0%) with pyrexia and 3 patients (15.0%) with hyperthermia in Table 18 were paediatric patients treated in Cohort 1 studies (MW2004-11-02 and MW2008-09-03; refer to PART II: Module SIII) (N = 20).

Routine preventive measures introducing soaking with antimicrobial solution to be performed for a minimum period of 2 hours before and after NexoBrid application as a measure to reduce the occurrence of wound infections and pyrexia has only been implemented at the time of later clinical studies MW2005-10-05, MW2008-09-03, MW2004-11-02, and MW2010-03-02 (DETECT), which resulted in higher incidence rate of pyrexia/hyperthermia-related events reported from the early clinical studies (MW2001-10-03 and MW2002-04-01).

The incidence of pyrexia/hyperthermia-related events by pre- and post-implementation of preventive measures in NexoBrid treatment group is presented in Table 19.

In the NexoBrid and placebo groups, the frequencies of overall fever events by combined preferred terms were more than twice as high pre-implementation compared to post-implementation of preventive measures, with pyrexia the primary contributor to the higher rate. Post-implementation, the frequency of pyrexia was still slightly higher in the NexoBrid (12.1%), compared to SOC (8.1%) and placebo (6.1%) treatment groups (ISS, Table 14.3.4.1.1.4).

[7] PTs for pyrexia/hyperthermia-related events were grouped by clinical inspection of the data and included pyrexia, hyperthermia, and body temperature increased.

Table 19: Pyrexia/Hyperthermia TEAEs in NexoBrid Treatment Group by Preferred Term and Pre- and Post-Implementation of Preventive Measures

Pyrexia/Hyperthermia TEAE (MedDRA PT)	Pre-Implementation Pool [a]	Post-Implementation Pool [b]
	NexoBrid (N = 77) n (%)	NexoBrid (N = 223) n (%)
Any pyrexia/hyperthermia TEAE	27 (35.1)	34 (15.2)
Body temperature increased	0	2 (0.9)
Hyperthermia	0	5 (2.2)
Pyrexia	27 (35.1)	27 (12.1)

Note: Subjects are counted only once in each MedDRA PT category.
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
[a] Studies MW2001-10-03 and MW2002-04-01.
[b] Studies MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02 (DETECT).
Source: ISS, Table 14.3.4.1.1a

There was a similar frequency of 'any pyrexia/hyperthermia TEAE' in the NexoBrid (15.3%) and SOC (12.1%) groups in Cohort 2 and there were 2 patients (8.3%) with pyrexia/hyperthermia-related events in the placebo group (Table 20).

In Cohort 1, the frequencies of patients with 'any pyrexia/hyperthermia TEAE'[7] in the NexoBrid and placebo groups (20.3% and 19.1%, respectively) were approximately double the frequency in the SOC group (10.8%), with MedDRA PT pyrexia being the primary contributor to the higher rate (Table 20).

Table 20: Summary of Any Pyrexia/Hyperthermia-Related TEAE by Cohort and Treatment Group (Pooled Safety Analysis Set)

Pain TEAE (MedDRA PT)	NexoBrid n (%)	SOC n (%)	Placebo n (%)
Cohort 1			
N	300	195	68
Any pyrexia/hyperthermia TEAE	61 (20.3)	21 (10.8)	13 (19.1)
Pyrexia	54 (18.0)	16 (8.2)	11 (16.2)
Hyperthermia	5 (1.7)	4 (2.1)	0
Body temperature increased	2 (0.7)	1 (0.5)	2 (2.9)
Cohort 2			
N	177	149	24
Any pyrexia/hyperthermia TEAE	27 (15.3)	18 (12.1)	2 (8.3)
Pyrexia	21 (11.9)	13 (8.7)	2 (8.3)
Hyperthermia	5 (2.8)	4 (2.7)	0
Body temperature increased	1 (0.6)	1 (0.7)	0

Note: Subjects are counted only once in each MedDRA PT category.
Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03

Table 20: Summary of Any Pyrexia/Hyperthermia-Related TEAE by Cohort and Treatment Group (Pooled Safety Analysis Set)

Pain TEAE (MedDRA PT)	NexoBrid n (%)	SOC n (%)	Placebo n (%)

Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; SOC = standard of care; TEAE = treatment-emergent adverse event.
Source: ISS, Tables 14.3.1.14.1a and 14.3.1.14.2

By MedDRA PT, the frequencies of pyrexia, hyperthermia, and increased body temperature were similar in the NexoBrid and SOC treatment groups in Cohort 2 (Table 20).

No events in NexoBrid treatment group of either Cohort were assessed as serious.

The majority of reported events in NexoBrid treatment group were mild to moderate in severity. One patient (0.3%) in Cohort 1 had a severe TEAE of pyrexia, assessed as not related to NexoBrid.

Of the patients with pyrexia/hyperthermia-related event (all treatment groups) in Cohort 2, approximately half experienced pyrexia during the treatment session in all 3 treatment groups. All patients in NexoBrid treatment group and almost all patients in all treatment groups experienced pyrexia/hyperthermia-related events during treatment or during the first week after treatment. Three patients in Cohort 2 experienced pyrexia during the 2 to 4 weeks after treatment (2 patients in NexoBrid and 1 patient in SOC treatment groups). Time to onset of pyrexia/hyperthermia-related TEAEs in Cohort 1 shows a similar pattern to Cohort 2.

12 Months and 24 Months Post Wound Closure (Study MW2010-03-02 [DETECT] Follow-Up Data)

No patient had a pyrexia/hyperthermia-related event in the time periods from 3 to 12 months or 12 to 24 months post wound closure.

Clinical Trials (Paediatric Population; SIII.2)

TEAEs were defined as adverse events that occurred after the start of treatment and up to 3 months post wound closure (i.e., acute phase). Additionally, the follow-up data for Study MW2012-01-01 (CIDS) are shown for the period from 12 weeks to 12 months post would closure.

Data are presented in this sub-section for the Study MW2012-01-01 (CIDS) and pooled populations (paediatric and adult) from the pooled studies (refer to SIII.2).

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Study MW2012-01-01 (CIDS): Acute Phase (Up to 12 Weeks Post Wound Closure)

The incidence rates of pyrexia/hyperthermia-related TEAEs[8] by treatment group are summarised in Table 21.

[8] PTs for pyrexia/hyperthermia-related events were grouped by clinical inspection of the data and included pyrexia, hyperthermia, and body temperature increased.

Table 21: Summary of Pyrexia/Hyperthermia TEAEs in Pivotal Study MW2012-01-01 (CIDS) by Treatment Group (0 to 12-Week Follow-Up Period)

TEAE (MedDRA PT)	NexoBrid (N = 69) n (%)	SOC (N = 70) n (%)
Any pyrexia/hyperthermia TEAE	8 (11.6)	4 (5.7)
Pyrexia	7 (10.1)	4 (5.7)
Hyperthermia	1 (1.4)	0

Note: Subjects are counted only once in each MedDRA PT category.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
Source: CIDS CSR, Table 14.3.1.1.2.5

One patient (1.4%) had a severe event of pyrexia assessed as serious. All other events were assessed as nonserious.

Overall, 2 patients (2.9%) had an event of pyrexia considered as severe. All other reported events were mild or moderate.

The frequency of 'any pyrexia/hyperthermia TEAE' was 11.6% in the NexoBrid and 5.7% in the SOC treatment groups (Table 21).

Study MW2012-01-01 (CIDS): 12 Weeks to 12 Months Post Wound Closure Follow-Up Data

No pyrexia/hyperthermia-related TEAE was reported in the period from 12 weeks to 12 months post wound closure.

Pooled Populations (Paediatric and Adult)

The incidence rates of 'any pyrexia/hyperthermia TEAE'[8] in the paediatric and adult pooled populations post-implementation of corrective procedures by treatment group 12 weeks post wound closure are provided in Table 22.

Table 22: Summary of Pyrexia/Hyperthermia TEAEs in the Paediatric and Adult Pooled Populations (Post-Implementation of Corrective Procedures) by Treatment Group (12 Weeks Post Wound Closure)

TEAE (MedDRA PT)	Paediatric Pooled Population [a]		Adult Pooled Population [b]		
	NexoBrid (N = 89) n (%)	SOC (N = 86) n (%)	NexoBrid (N = 203) n (%)	SOC (N = 144) n (%)	Placebo (N = 33) n (%)
Any pyrexia/hyperthermia TEAE	15 (16.9)	8 (9.3)	27 (13.3)	14 (9.7)	2 (6.1)
Pyrexia	11 (12.4)	7 (8.1)	23 (11.3)	10 (6.9)	2 (6.1)
Hyperthermia	4 (4.5)	1 (1.2)	2 (1.0)	3 (2.1)	0
Body temperature increased	0	0	2 (1.0)	1 (0.7)	0

Note: Subjects are counted only once in each MedDRA PT category.
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
[a] Studies MW2012-01-01 [CIDS], MW2008-09-03, and MW2004-11-02 (paediatric patients only)
[b] Studies MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02 (adult patients only)
Source: ISS, Table 14.3.1.7.1.1

There was no significant difference in the incidence of 'any pyrexia/hyperthermia TEAE' between the adult pooled population post-implementation of corrective procedures and paediatric population in study MW2012-01-01 (CIDS) (13.3% and 11.6%, respectively; Table 22 and Table 21). Two patients in the paediatric pooled population had severe event of pyrexia, of which one was further assessed as serious. No serious event was reported in the adult pooled population.

The incidence of 'any pyrexia/hyperthermia TEAE' in the paediatric pooled population was higher in the NexoBrid group in comparison to the SOC group (16.9% versus 9.3%) and also in comparison to the adult pooled population post-implementation of corrective procedures (16.9% versus 13.3%) (Table 22). Since children with burn injury are in general more prone to fever than adults (Kim et al, 1998; Gore et al, 2003; Sarginson et al, 2021), the difference in the incidence rates between paediatric and adult pooled populations is not unexpected.

There were no noteworthy trends in distribution of pyrexia/hyperthermia TEAEs across the age groups in paediatric population. The number of paediatric patients with pyrexia/hyperthermia TEAEs was moderate across all age groups in either treatment arm.

Impact on Quality of Life

Pyrexia/hyperthermia, especially in their severe forms, may significantly reduce the quality of patient's life during the burn trauma treatment. Hyperthermia in burn patients has been shown to further heighten the hypermetabolic state (Gore et al, 2003; Bayuo, 2017).

Post-Marketing Experience

Evaluation of data collected from the post marketing experience (spontaneous and solicited sources of information) did not identify any new and significant information and these data are in line with the safety profile of NexoBrid from the development programme.

Cumulatively since the IBD until 17 December 2021[9], 2 ADRs of pyrexia/hyperthermia were reported from spontaneous post-marketing sources in valid individual case safety reports. This represents a reporting rate of 0.02%, considering the total post-marketing patient exposure of 8,828 patients (refer to Section SV.1.2).

Of the patients analysed in the retrospective, non-interventional PASS MW2013-06-01 (NexoPASS) completed in 2019 (N = 164), pyrexia[10] within 48 hours from start of NexoBrid treatment was reported in 6 patients (3.7%). Same incidence rate was observed for the onset of pyrexia within 72 hours post treatment. The compliance rate of 52.7% was shown for required antibacterial soaking applied before NexoBrid and 57.8% for antibacterial soaking applied after NexoBrid.

[9] The date represents the data lock point for the Addendum to Clinical Overview submitted for the second renewal of the marketing authorisation for NexoBrid, providing the most up-to-date post-marketing data for NexoBrid.

[10] Pyrexia was defined as 'temperature > 38.5°C within 48 hours from start of NexoBrid treatment requiring fever relief medications prescribed due to high temperature within 1 hour from complaint, consecutive measurements of high temperature (> 38.5°C), 4 to 6 hours apart.'

According to worst-case analysis[11], pyrexia within 48 hours from start of NexoBrid treatment was observed in 23 patients (14.0%), of which in 10 patients (6.1%) was assessed as related to NexoBrid.

None of the pyrexia-associated events was assessed as serious.

Risk Factors and Risk Groups:

There are several different risk factors for the development of pyrexia/hyperthermia in burn patients, such as wound infection or contaminated wound (Mavrogordato et al, 2009)., and other infections, including pneumonia or urinary tract infection (D'Avignon and Murray).

Children with burn injury are in general more susceptible to fever (Kim et al, 1998; Gore et al, 2003; Sarginson et al, 2021).

Preventability:

The wound must be cleaned thoroughly. Dressing soaked with antibacterial solution must be applied for 2 hours prior to administration of NexoBrid and after its removal from the target wound.

Refer to Part V.2 for a detailed description of the additional risk minimisation measures in place, designed to further mitigate the risk of pyrexia/hyperthermia in burn patients treated with NexoBrid.

Impact on the Risk-Benefit Balance of the Product:

Considering the significant impact of pyrexia/hyperthermia on burn patients, this risk represents an important identified risk of NexoBrid. In general, this risk can be anticipated and managed in the clinical setting. The highly effective risk minimisation measures are in place, making the overall impact of this risk on the product acceptable in the light of the anticipated benefits to burn patients.

Public Health Impact:

It is anticipated that more than 1 in 10 patients treated with NexoBrid in the post-marketing setting will experience pyrexia/hyperthermia.

Considering the low overall incidence of deep burn injuries and the eligibility criteria to NexoBrid treatment, the public health impact of this risk occurring in association with NexoBrid therapy is considered low.

SVII.3.1.3 Important Identified Risk 3: Wound Complications (Including Wound Infections)

Potential Mechanism(s):

Wound healing is a complex process in which the burn patient's immune system plays an important role (Markiewicz-Gospodarek et al, 2022). Various wound complication have been described in burn patients, including impaired healing, delayed time to complete wound closure (TTCWC), or wound infections (Church et al, 2006).

[11] Sensitivity analyses were conducted to assess robustness of the study results, i.e., best-case analyses with subjects treated in compliance with the educational materials and worst-case analyses, based on an incidence rate for which each 'possible' adverse event of interest is regarded as a definite adverse event of interest.

The burn wound is susceptible to opportunistic colonisation by organisms of endogenous and exogenous origin (Church et al, 2006). Severe burn patients have a high risk for developing burn wound sepsis (Norbury et al, 2016).

Evidence Source(s) and Strength of Evidence:

Various wound complications, including a delay in TTCWC (in certain cases linked to a selected wound-care strategy) and wound infections, were reported in early clinical development programme for NexoBrid. The implementation of preventive measures later in the programme led to a decrease in the incidence of general wound infections. However, wound complications (including wound infections) remain an important risk associated with NexoBrid treatment.

Characterisation of the Risk:

Clinical Trials (Pooled Safety Analysis Set - Cohort 1 and Cohort 2 Studies; SIII.1)

'All TEAEs' were defined as those events that occurred in clinical studies after the start of treatment (NexoBrid, SOC, or placebo [gel vehicle]) and up to 3 months post wound closure of all treated wounds (i.e., acute phase) with the exception of Study MW2005-10-05, which was 1 month post wound closure.

Data from the 12- and 24-month follow-up in Study MW2010-03-02 (DETECT) are presented separately.

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Acute Phase (Up to 3 Months Post Wound Closure)

The incidence rates of wound complications/infections-related TEAEs[12] in NexoBrid treatment group by study cohort are summarised in Table 23.

Table 23: Summary of TEAEs and NexoBrid-Related TEAEs of Wound Complications (Including Wound Infections) in NexoBrid Treatment Group by Study Cohorts (Pooled Safety Analysis Set)

TEAE (MedDRA PT)	Cohort 2 (N = 177) n (%)		Cohort 1 (N = 300) n (%)	
	All TEAEs	Related	All TEAEs	Related
Wound infections				
Wound infection	8 (4.5)	1 (0.6)	13 (4.3)	1 (0.3)
Wound infections by grouped PTs[a]	11 (6.2)	1 (0.6)	18 (6.0)	1 (0.3)
Wound fungal infection by grouped PTs[b]	3 (1.7)	0	3 (1.0)	0

[12] PTs for wound-related infection events were grouped by clinical inspection of the data and included the following terms (if reported as local target wound-related events): wound infection, infection, wound infection bacterial, staphylococcal infection, burn infection, proteus infection, bacterial infection, staphylococcal skin infection, wound infection staphylococcal, localised infection, candida infection, fungal infection, fungal skin infection, and wound infection fungal.

For wound-related complications, various terms associated with the wound, scar, or graft were included in the search strategy, if reported as local target wound-related events. Full search strategy for the risk of wound complications (including wound infections) is provided in Annex 7.

Table 23: Summary of TEAEs and NexoBrid-Related TEAEs of Wound Complications (Including Wound Infections) in NexoBrid Treatment Group by Study Cohorts (Pooled Safety Analysis Set)

TEAE (MedDRA PT)	Cohort 2 (N = 177) n (%)		Cohort 1 (N = 300) n (%)	
	All TEAEs	Related	All TEAEs	Related
Wound complications				
Graft loss	3 (1.7)	1 (0.6)	3 (1.0)	1 (0.3)
Impaired healing	0	0	1 (0.3)	0
Scar	2 (1.1)	0	2 (0.7)	0
Skin graft failure	4 (2.3)	0	6 (2.0)	1 (0.3)
Skin graft infection	1 (0.6)	0	1 (0.3)	0
Wound complication	5 (2.8)	1 (0.6)	9 (3.0)	1 (0.3)
Wound decomposition	3 (1.7)	0	3 (1.0)	0
Wound necrosis	0	0	1 (0.3)	0

Note: Subjects are counted only once in each MedDRA PT category.
Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03
Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
[a] Grouped PTs of wound infection, infection, wound infection bacterial, staphylococcal infection, burn infection, proteus infection, bacterial infection, staphylococcal skin infection, wound infection staphylococcal, and localised infection.
[b] Grouped PTs of candida infection, fungal infection, fungal skin infection, and wound infection fungal.
Source: ISS, Tables 14.3.1.12.1a, 14.3.1.12.2, 14.3.1.13.1a, 14.3.1.13.2, 14.3.1.2.1a, 14.3.1.2.2, 14.3.1.5.1a, and 14.3.1.5.2

One patient (1/20; 5.0%) with skin graft failure in Table 23 was a paediatric patient treated in Cohort 1 studies (MW2004-11-02 and MW2008-09-03; refer to PART II: Module SIII) (N = 20).

Routine preventive measures introducing soaking with antimicrobial solution to be performed for a minimum period of 2 hours before and after NexoBrid application as a measure to reduce the occurrence of wound infections and pyrexia has only been implemented at the time of later clinical studies MW2005-10-05, MW2008-09-03, MW2004-11-02, and MW2010-03-02 (DETECT). Therefore, the incidence of wound infection-related events by pre- and post-implementation of preventive measures is presented in Table 24.

In the NexoBrid treatment group, the frequencies of patients with overall wound infection events by grouped PTs were slightly higher pre-implementation compared to post-implementation of preventive measures (7.8% versus 5.4% for infections excluding fungal) (Table 24).

Post-implementation of preventive measures, the frequencies of patients with infection were similar in the NexoBrid and SOC treatment groups (5.4% and 8.1%, respectively, for infections excluding fungal and 1.3% and 0, respectively, for fungal infections) (ISS, Table 14.3.4.1.1.4).

Table 24: Wound Infection TEAEs in NexoBrid Treatment Group by Pre- and Post-Implementation of Preventive Measures

Pain TEAE (MedDRA PT)	Pre-Implementation Pool[a]	Post-Implementation Pool[b]
	NexoBrid (N = 77) n (%)	NexoBrid (N = 223) n (%)
Bacterial infections	**6 (7.8)**	**12 (5.4)**
Wound infection	5 (6.5)	8 (3.6)
Wound infection bacterial	0	3 (1.3)
Infection	0	1 (0.4)
Burn infection	1 (1.3)	0
Staphylococcal infection	0	0
Staphylococcal skin infection	0	0
Wound infection staphylococcal	0	0
Fungal infections	**0**	**3 (1.3)**
Fungal infection	0	1 (0.4)
Fungal skin infection	0	1 (0.4)
Wound infection fungal	0	1 (0.4)

Note: Subjects are counted only once in each MedDRA PT category.
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
[a] Studies MW2001-10-03 and MW2002-04-01.
[b] Studies MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02 (DETECT).
Source: ISS, Table 14.3.4.1.1a

There was a similar frequency of wound-related infections in the NexoBrid and SOC treatment groups in Cohort 2 across all 3 groupings of PTs for wound infection[12] (Table 25). In Cohort 1, as in Cohort 2, there was a similar frequency of wound-related infections in the NexoBrid and SOC treatment groups across all 3 groupings[12] (Table 25).

Table 25: Summary of Any Wound Infection-Related TEAE by Cohort and Treatment Group (Pooled Safety Analysis Set)

Pain TEAE (MedDRA PT)	NexoBrid n (%)	SOC n (%)	Placebo n (%)
Cohort 1			
N	300	195	68
Wound infection	13 (4.3)	6 (3.1)	3 (4.4)
Wound infections by grouped PTs[a]	18 (6.0)	13 (6.7)	5 (7.4)
Wound fungal infection by grouped PTs[b]	3 (1.0)	0	0
Cohort 2			
N	177	149	24
Wound infection	8 (4.5)	6 (4.0)	0
Wound infections by grouped PTs[a]	11 (6.2)	13 (8.7)	0
Wound fungal infection by grouped PTs[b]	3 (1.7)	0	0

Note: Subjects are counted only once in each MedDRA PT category.

Table 25: Summary of Any Wound Infection-Related TEAE by Cohort and Treatment Group (Pooled Safety Analysis Set)

Pain TEAE (MedDRA PT)	NexoBrid n (%)	SOC n (%)	Placebo n (%)

Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03
Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; SOC = standard of care; TEAE = treatment-emergent adverse event.
[a] Grouped PTs of wound infection, infection, wound infection bacterial, staphylococcal infection, burn infection, proteus infection, bacterial infection, staphylococcal skin infection, wound infection staphylococcal, and localised infection.
[b] Grouped PTs of candida infection, fungal infection, fungal skin infection, and wound infection fungal.
Source: ISS, Tables 14.3.1.12.1a and 14.3.1.12.2

Two patients (1.1%) in the NexoBrid treatment group of Cohort 2 (and also Cohort 1) had event of wound infection bacterial assessed as serious. No other serious events were reported.

In Cohort 2, 4 patients had wound infection during treatment (1 patients in the NexoBrid and 3 patients in the SOC treatment groups), 6 patients had wound infection during week 2 up to week 8 (2 in the NexoBrid and 4 in the SOC treatment groups). All other patients were missing an onset evaluation. In Cohort 1, there was a similar pattern in time to onset of wound infections compared with in Cohort 2.

Time to Wound Closure

TTCWC was slightly longer in the NexoBrid group than in the SOC group of Cohort 2, when estimated by the Kaplan-Meier method (median of 30.0 days versus 25.0 days) or calculated using actual data (mean of 31.7 days versus 29.8 days, median of 25.0 days versus 24.0 days). According to the non-inferiority analysis, TTCWC was less than 7 days longer with NexoBrid than with SOC (p for non-inferiority=0.0006).

In Cohort 1, TTCWC was slightly longer in the NexoBrid group than in the SOC group, when estimated by the Kaplan-Meier method (median of 31.0 days versus 27.0 days) or calculated using actual data (mean of 32.5 days versus 30.4 days, median of 28.0 days versus 24.0 days). According to the non-inferiority analysis, TTCWC was less than 7 days longer with NexoBrid than with SOC (p for non-inferiority=0.0005).

Altogether, the results of the analysis of TTCWC along with the finding that maintenance of complete wound closure was generally similar across the treatment groups demonstrate that NexoBrid does not have a deleterious effect on wound closure.

It is important to note that the time to wound closure is affected by the decision of the treating physician who is responsible for making the decision of autografting DPT wounds immediately after debridement (which could result in faster wound closure in patients treated with NexoBrid due to the earlier debridement) or allowing spontaneous epithelisation (which would not require autografting or donor sites sacrifice, but would likely result in longer TTCWC with less pain and donor site scarring).

12 Months and 24 Months Post Wound Closure (Study MW2010-03-02 [DETECT] Follow-Up Data)

Only a single patient (1.3%) in the NexoBrid treatment group reported an event of staphylococcal skin infection (target wound-related event) during the time period from 3 to 12 months post wound closure, assessed as non-serious and unrelated to NexoBrid.

No patient had a wound complication/wound infection event in the time period from 12 to 24 months post wound closure.

Clinical Trials (Paediatric Population; SIII.2)

TEAEs were defined as adverse events that occurred after the start of treatment and up to 3 months post wound closure (i.e., acute phase). Additionally, the follow-up data for Study MW2012-01-01 (CIDS) are shown for the period from 12 weeks to 12 months post would closure.

Data are presented in this sub-section for the Study MW2012-01-01 (CIDS) and pooled populations (paediatric and adult) from the pooled studies (refer to SIII.2).

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Study MW2012-01-01 (CIDS): Acute Phase (Up to 12 Weeks Post Wound Closure)

The incidence rates of wound complications/infections-related TEAEs[13] by treatment group are summarised in Table 26.

Table 26: Summary of Wound Complications (Including Wound Infections) TEAEs of in Pivotal Study MW2012-01-01 (CIDS) by Treatment Group (0 to 12-Week Follow-Up Period)

TEAE (MedDRA PT)	NexoBrid (N = 69) n (%)	SOC (N = 70) n (%)
Wound infections		
Any wound infection TEAE	1 (1.4)	3 (4.3)
Culture wound positive	1 (1.4)	1 (1.4)
Wound infection	0	2 (2.9)
Wound complications		
Wound complication	5 (7.2)	5 (7.1)
Graft loss	0	1 (1.4)
Wound dehiscence	0	1 (1.4)
Wound haemorrhage	0	1 (1.4)

[13] Wound-related infection events were grouped by clinical inspection of the data and included the following terms (if reported as local target wound-related events): wound infection, infection, wound infection bacterial, staphylococcal infection, burn infection, proteus infection, bacterial infection, staphylococcal skin infection, wound infection staphylococcal, localised infection, candida infection, fungal infection, fungal skin infection, and wound infection fungal.

For wound-related complications, various terms associated with the wound, scar, or graft were included in the search strategy, if reported as local target wound-related events. Full search strategy for the risk of wound complications (including wound infections) is provided in Annex 7.

Table 26: Summary of Wound Complications (Including Wound Infections) TEAEs of in Pivotal Study MW2012-01-01 (CIDS) by Treatment Group (0 to 12-Week Follow-Up Period)

TEAE (MedDRA PT)	NexoBrid (N = 69) n (%)	SOC (N = 70) n (%)

Note: Subjects are counted only once in each MedDRA PT category.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
Source: CIDS CSR, Tables 14.3.1.1.2.6 and 14.3.1.1.2.1

None of these events were assessed as serious. All events were mild or moderate in severity.

The frequency of 'any target wound-associated TEAE' of wound infection was 1.4% in the NexoBrid and 4.3% in the SOC treatment groups (Table 26).

Study MW2012-01-01 (CIDS): 12 Weeks to 12 Months Post Wound Closure Follow-Up Data

Two patients (2.9%) in the NexoBrid treatment group reported a TEAE of wound complication (verbatim terms of 'itching of target wound 1, 2, and 3' and 'itching of target wounds'), during the follow-up period from 12 weeks until 12 months post wound closure.

There were no TEAEs considered as related to NexoBrid in the period from 12 weeks to 12 months post wound closure.

Pooled Populations (Paediatric and Adult)

The incidence rates of 'wound infection/complication TEAE'[13] in the paediatric and adult pooled populations post-implementation of corrective procedures by treatment group 12 weeks post wound closure are provided in Table 27.

Table 27: Summary of Wound Complications (Including Wound Infections) TEAEs in the Paediatric and Adult Pooled Populations (Post Implementation of Corrective Procedures) by Treatment Group (12 Weeks Post Wound Closure)

TEAE (MedDRA PT)	Paediatric Pooled Population [a]		Adult Pooled Population [b]		
	NexoBrid (N = 89) n (%)	SOC (N = 86) n (%)	NexoBrid (N = 203) n (%)	SOC (N = 144) n (%)	Placebo (N = 33) n (%)
Wound infections					
Any wound infection TEAE	1 (1.1)	7 (8.1)	12 (5.9)	9 (6.3)	0
Culture wound positive	1 (1.1)	1 (1.2)	0	0	0
Staphylococcal infection	0	1 (1.2)	0	0	0
Wound infection	0	5 (5.8)	8 (3.9)	3 (2.1)	0
Wound infection bacterial	0	0	3 (1.5)	4 (2.8)	0
Infection	0	0	1 (0.5)	0	0
Staphylococcal skin infection	0	0	0	1 (0.7)	0
Wound infection staphylococcal	0	0	0	1 (0.7)	0

Table 27: Summary of Wound Complications (Including Wound Infections) TEAEs in the Paediatric and Adult Pooled Populations (Post Implementation of Corrective Procedures) by Treatment Group (12 Weeks Post Wound Closure)

TEAE (MedDRA PT)	Paediatric Pooled Population [a]		Adult Pooled Population [b]		
	NexoBrid (N = 89) n (%)	SOC (N = 86) n (%)	NexoBrid (N = 203) n (%)	SOC (N = 144) n (%)	Placebo (N = 33) n (%)
Any fungal wound infection	0	0	3 (1.5)	0	0
Fungal infection	0	0	1 (0.5)	0	0
Fungal skin infection	0	0	1 (0.5)	0	0
Wound infection fungal	0	0	1 (0.5)	0	0
Wound complications					
Wound complication	5 (5.6)	5 (5.8)	6 (3.0)	2 (1.4)	0
Skin graft failure	1 (1.1)	1 (1.2)	3 (1.5)	0	0
Graft loss	0	1 (1.2)	3 (1.5)	3 (2.1)	1 (3.0)
Wound decomposition	0	1 (1.2)	3 (1.5)	1 (0.7)	0
Wound dehiscence	0	1 (1.2)	0	0	0
Wound haemorrhage	0	1 (1.2)	0	0	0
Graft complication	0	0	0	1 (0.7)	0
Scar	0	0	2 (1.0)	0	0
Skin graft infection	0	0	1 (0.5)	0	0

Note: Subjects are counted only once in each MedDRA PT category.
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event
[a] Studies MW2012-01-01 [CIDS], MW2008-09-03, and MW2004-11-02 (paediatric patients only)
[b] Studies MW2004-11-02, MW2005-10-05, MW2008-09-03, and MW2010-03-02 (adult patients only)
Source: ISS, Tables 14.3.1.2.1.1, 14.3.1.7.1.1, and 14.3.1.2.1.3

The incidence rate of 'any wound infection TEAE' was 1.1% in the NexoBrid group and 8.1% in the SOC group of the paediatric pooled population (Table 27). The incidence rates of wound complications were similar between the paediatric pooled population and the adult pooled population post-implementation of corrective procedures, while the incidence rates of wound infections were higher in the adult pooled population in comparison to the paediatric pooled population (Table 27).

No patient in the paediatric pooled population had event assessed as serious in comparison to 2 patients in the adult pooled population.

There were no noteworthy trends in distribution of wound infection TEAEs across the age groups in paediatric population. The number of paediatric patients with wound infection TEAEs was low across all age groups in either treatment arm.

Time to Wound Closure

In the main analysis in study MW2012-01-01 (CIDS), the TTCWC on a target wound level was comparable in the NexoBrid and SOC treatment groups. The Kaplan-Meier estimated

median TTCWC for NexoBrid and SOC on a target wound level (clustered data of target wounds in a patient) was 32 days and 41 days, respectively.

Statistical analysis established the noninferiority of NexoBrid compared with SOC when incorporating a 7-day advantage for the SOC treatment group. However, the difference in the estimated median time for NexoBrid compared with SOC also exceeded the 7-day advantage incorporated for SOC in the statistical analyses.

In an additional analysis, the Kaplan-Meier estimate TTCWC on a patient level was also numerically shorter in the NexoBrid group (32 days) than under the SOC (41 days) incorporating a 7-day advantage for SOC; however, the noninferiority in the statistical analyses was not established.

Time to 100% wound closure in NexoBrid and SOC treated patients was comparable between the MW2012-01-01 (CIDS) study and paediatric pooled or adult pooled populations.

In the paediatric pooled population, the time to reach 100% wound closure was slightly shorter in the NexoBrid group than in the SOC group, when estimated by the Kaplan-Meier method: 41 days (95% confidence interval [CI]: 30.0 to 61.0) versus 50 days (95% CI: 35.0 to 71.0).

In the adult pooled population, the time to reach 100% wound closure was slightly longer in the NexoBrid group than in the SOC group, when estimated by the Kaplan-Meier method: 39 days (95% CI: 34.0 to 43.0) versus 36 days (95% CI: 33.0 to 38.0).

Impact on Quality of Life

Severe wound complications may prolong the time and overall success of wound healing in burn patients.

Sepsis due to wound infections can be a life-threatening condition with fatal outcomes.

Post-Marketing Experience

Evaluation of data collected from the post marketing experience (spontaneous and solicited sources of information) did not identify any new and significant information and these data are in line with the safety profile of NexoBrid from the development programme.

Cumulatively since the IBD until 17 December 2021[14], 7 ADRs of wound complications (including wound infections)[15] were reported from spontaneous post-marketing sources in valid individual case safety reports. This represents a reporting rate of 0.08%, considering the total post-marketing patient exposure of 8,828 patients (refer to Section SV.1.2).

In the retrospective, non-interventional PASS MW2013-06-01 (NexoPASS) completed in 2019, the median TTCWC was 42.0 days at the patient level. At the wound level, the median TTCWC was 39.0 days and results were comparable between wounds treated with NexoBrid and SOC procedures.

Of all patients analysed in this study (N = 164), wound-related complications were identified in 2 patients (1.2%), based on events of unknown or at least possible relatedness

[14] The date represents the data lock point for the Addendum to Clinical Overview submitted for the second renewal of the marketing authorisation for NexoBrid, providing the most up-to-date post-marketing data for NexoBrid.

[15] PTs wound complication, wound infection, and impaired healing

to NexoBrid. Both patients suffered from graft loss assessed by the investigator as possibly related to NexoBrid.

Wound infection[16] within 1 week from start of debridement was observed in 12 patients (7.3%). However, no wound infection was assessed as related to the NexoBrid treatment.

According to worst-case analysis[17], wound infection within 1 week from start of debridement was observed in 51 patients (31.1%).

Risk Factors and risk Groups:

Patients with burn area greater than 30% TBSA or old, contaminated burns are at increased risk of wound complications, same as burn patients with FT wounds and deep burns that cannot spontaneously epithelise and are not autografted immediately after debridement for TTCWC.

Immunosuppressed patients are in general at higher risk of wound infections and sepsis (Church et al, 2006).

Preventability:

Routine preventive measures include soaking of the target wound with antimicrobial solution for a minimum period of 2 hours before and after NexoBrid application.

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 brushing or scraping to allow dressing adherence.

Refer to Part V.2 for a detailed description of the additional risk minimisation measures in place designed to mitigate this risk in burn patients treated with NexoBrid.

Impact on the Risk-Benefit Balance of the Product:

Wound complications, including infections, could impact the treatment in burn patients. The risks can be anticipated and managed in the clinical setting. The impact of this risk on the benefit-risk balance of NexoBrid is acceptable in the light of the anticipated benefits to burn patients.

Public Health Impact:

It is anticipated that ≥1 in 100 to <1 in 10 patients treated with NexoBrid in the post-marketing setting will experience wound infection or wound complication.

Considering the low overall incidence of deep burn injuries and the eligibility criteria to NexoBrid treatment, the public health impact of this risk occurring in association with NexoBrid therapy is considered low.

[16] Wound infection was defined as 'prescription of antibiotics during the first week following debridement with NexoBrid to a patient captured with positive swabs and/or positive wound biopsies performed'.

[17] Sensitivity analyses were conducted to assess robustness of the study results, i.e., best-case analyses with subjects treated in compliance with the educational materials and worst-case analyses, based on an incidence rate for which each 'possible' adverse event of interest is regarded as a definite adverse event of interest.

SVII.3.1.4 Important Identified Risk 4: Allergic Reactions (Including Anaphylactic Reaction)

Potential Mechanism(s):

Bromelain is mostly implicated in IgE-mediated allergies of both the immediate type and the late-phase of immediate type (Gailhofer et al, 1988; Kelly, 1996). A skin contact with pure allergen can trigger a systemic reaction in susceptible individuals (Gailhofer et al, 1988).

Evidence Source(s) and Strength of Evidence:

Allergic reactions associated with NexoBrid application, including infrequent events of anaphylactic reaction, were reported from the post-marketing experience with NexoBrid.

Allergic reactions to bromelain have been reported in the literature, mostly related to cases of airway sensitisation resulting from occupational exposure (Baur and Fruhmann, 1979; Gailhofer et al, 1988; van Kampen et al, 2007) or general pineapple allergy (Knox et al, 2019; Kiguchi et al, 2021).

Characterisation of the Risk:

Clinical Trials (Pooled Safety Analysis Set - Cohort 1 and Cohort 2 Studies; SIII.1)

'All TEAEs' were defined as those events that occurred in clinical studies after the start of treatment (NexoBrid, SOC, or placebo [gel vehicle]) and up to 3 months post wound closure of all treated wounds (i.e., acute phase) with the exception of Study MW2005-10-05, which was 1 month post wound closure.

Data from the 12- and 24-month follow-up in Study MW2010-03-02 (DETECT) are presented separately.

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Acute Phase (Up to 3 Months Post Wound Closure)

The incidence rates of TEAEs[18] meeting the search strategy for allergic reactions in NexoBrid treatment group by study cohort are summarised in Table 28.

[18] The standardised MedDRA queries (SMQs) Anaphylactic reaction and Hypersensitivity were used to identify respective events.

Additionally, SMQs of Angioedema, Eosinophilic pneumonia, and Periorbital and eyelid disorders and all events falling into the system organ class of Immune system disorders were searched for relevancy.

Table 28: Summary of TEAEs and NexoBrid-Related TEAEs within the SMQs Anaphylactic Reactions, Hypersensitivity, and Angioedema in NexoBrid Treatment Group by Study Cohorts (Pooled Safety Analysis Set)

TEAE (MedDRA PT)	Cohort 2 NexoBrid (N = 177) n (%)		Cohort 1 NexoBrid (N = 300) n (%)	
	All TEAEs	Related	All TEAEs	Related
Allergy to arthropod sting	1 (0.6)	0	1 (0.3)	0
Anaphylactic shock	1 (0.6)	0	1 (0.3)	0
Dermatitis allergic	0	0	1 (0.3)	0
Drug hypersensitivity	2 (1.1)	1 (0.6)	3 (1.0)	1 (0.3)
Erythema	1 (0.6)	0	1 (0.3)	0
Pruritus	27 (15.3)	2 (1.1)	35 (11.7)	2 (0.7)
Rash	6 (3.4)	2 (1.1)	9 (3.0)	2 (0.7)

Note: Subjects are counted only once in each MedDRA PT category.
Cohort 1 studies: MW2010-03-02 (DETECT), MW2004-11-02, MW2002-04-01, MW2005-10-05, MW2008-09-03, and MW2001-10-03
Cohort 2 studies: MW2010-03-02 (DETECT) and MW2004-11-02
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; TEAE = treatment-emergent adverse event.
Source: ISS, Tables 14.3.1.2.1a, 14.3.1.2.2, 14.3.1.5.1a, and 14.3.1.5.2

Six patients (6/20; 30.0%) with pruritus and 2 patients (10.0%) with rash in Table 28 were paediatric patients treated in Cohort 1 studies (MW2004-11-02 and MW2008-09-03; refer to PART II: Module SIII) (N = 20).

No TEAE of anaphylactic reaction related to NexoBrid occurred in the clinical development programme in either Cohort. A single patient in Cohort 2 in NexoBrid treatment group experienced anaphylactic shock 22 days after NexoBrid treatment, related to latex allergy.

Only 2 events of pruritus were assessed as related to NexoBrid, since pruritus, known as post-burn pruritus, is a common complication of burn injury, which severely lowers the quality of life of the patient. Post-burn pruritus occurs shortly after burn during the rehabilitation and healing process of burn wounds with a very high prevalence (80% to 100%) (Chung et al, 2020).

12 Months and 24 Months Post Wound Closure (Study MW2010-03-02 [DETECT] Follow-Up Data)

Four patients (5.2%) had AE of pruritus assessed as not related to NexoBrid during the time period from 3 to 12 months post wound closure.

No patient had allergic reactions-related AE in the time period from 12 to 24 months post wound closure.

Clinical Trials (Paediatric Population; SIII.2)

TEAEs were defined as adverse events that occurred after the start of treatment and up to 3 months post wound closure (i.e., acute phase). Additionally, the follow-up data for Study MW2012-01-01 (CIDS) are shown for the period from 12 weeks to 12 months post would closure.

Data are presented in this sub-section for the Study MW2012-01-01 (CIDS) and pooled populations (paediatric and adult) from the pooled studies (refer to SIII.2).

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Study MW2012-01-01 (CIDS): Acute Phase (Up to 12 Weeks Post Wound Closure)

The incidence rates of TEAEs[19] meeting the search strategy for allergic reactions by treatment group are summarised in Table 29.

Table 29: Summary of TEAEs within the SMQs Anaphylactic Reactions, Hypersensitivity, and Angioedema in Pivotal Study MW2012-01-01 (CIDS) by Treatment Group (0 to 12-Week Follow-Up Period)

TEAE (MedDRA PT)	NexoBrid (N = 69) n (%)	SOC (N = 70) n (%)
Erythema	1 (1.4)	0
Peripheral swelling	1 (1.4)	1 (1.4)
Pruritus	9 (13.0)	7 (10.0)
Rash	2 (2.9)	0
Rash maculo-papular	1 (1.4)	1 (1.4)
Seasonal allergy	1 (1.4)	1 (1.4)
Skin exfoliation	1 (1.4)	0

Note: Subjects are counted only once in each MedDRA PT category.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; SMQ = standardised MedDRA Query; SOC = standard of care; TEAE = treatment-emergent adverse event
Source: CIDS CSR, Table 14.3.1.1.2.1

The only hypersensitivity events that occurred within a day after study treatment were 4 cases of pruritus treated with antihistamines, and one case of local rash treated with topical hydrocortisone. One event of local rash and one event of local pruritus (reported in a single patient each) were considered as related to NexoBrid.

No events of anaphylactic reaction or any serious events were reported.

[19] The standardised MedDRA queries (SMQs) Anaphylactic reaction and Hypersensitivity were used to identify respective events.

Additionally, SMQs of Angioedema, Eosinophilic pneumonia, and Periorbital and eyelid disorders, Shock-associated circulatory or cardiac conditions (excluding torsade de pointes) and all events falling into the system organ class of Immune system disorders were searched for relevancy.

Study MW2012-01-01 (CIDS): 12 Weeks to 12 Months Post Wound Closure Follow-Up Data

One patient each (1.4%) reported seasonal allergy, rash and urticaria within the period from 12 weeks to 12 months post wound closure.

There were no TEAEs considered as related to NexoBrid in the period from 12 weeks to 12 months post wound closure.

Pooled Populations (Paediatric and Adult)

The incidence rates of TEAEs meeting the search strategy for allergic reactions[18,19] in the paediatric and adult pooled populations post-implementation of corrective procedures by treatment group 12 weeks post wound closure are provided in Table 30.

Table 30: Summary of TEAEs within the SMQs Anaphylactic Reactions, Hypersensitivity, and Angioedema in the Paediatric and Adult Pooled Populations (Post Implementation of Corrective Procedures) by Treatment Group (12 Weeks Post Wound Closure)

TEAE (MedDRA PT)	Paediatric Pooled Population [a]		Adult Pooled Population [b]		
	NexoBrid (N = 89) n (%)	SOC (N = 86) n (%)	NexoBrid (N = 203) n (%)	SOC (N = 144) n (%)	Placebo (N = 33) n (%)
Pruritus	15 (16.9)	8 (9.3)	27 (13.3)	25 (17.4)	8 (24.2)
Rash	4 (4.5)	0	6 (3.0)	0	0
Erythema	1 (1.1)	0	1 (0.5)	1 (0.7)	0
Peripheral swelling	1 (1.1)	1 (1.2)	1 (0.5)	0	0
Rash maculo-papular	1 (1.1)	1 (1.2)	0	0	0
Seasonal allergy	1 (1.1)	1 (1.2)	0	1 (0.7)	0
Skin exfoliation	1 (1.1)	0	1 (0.5)	0	0
Swelling face	0	1 (1.2)	0	0	0
Urticaria	0	1 (1.2)	0	0	0
Allergy to arthropod sting	0	0	1 (0.5)	0	0
Anaphylactic shock	0	0	1 (0.5)	0	0
Dermatitis allergic	0	0	0	0	0
Drug hypersensitivity	0	0	2 (1.0)	0	0
Hypersensitivity	0	0	0	1 (0.7)	0

Note: Subjects are counted only once in each MedDRA PT category.
ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of patients; N = total number of patients; PT = preferred term; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event
[a] Studies MW2012-01-01 [CIDS], MW2008-09-03, and MW2004-11-02 (paediatric patients only)
[b] Studies MW2004-11-02, MW2005-10-05, MW2008-09-03 and MW2010-03-02 (adult patients only)
Source: ISS, Table 14.3.1.1.2.1 and 14.3.1.2.1.3

There was no significant difference in the allergic reactions-related TEAEs between the paediatric and adult pooled populations post-implementation of corrective procedures and paediatric population in study MW2012-01-01 (CIDS) (Table 30 and Table 29, respectively).

No events of anaphylactic reaction or any serious events were reported in paediatric pooled population.

Impact on Quality of Life

Severe allergic reactions can quickly develop into life-threatening conditions with potentially fatal outcomes, if not appropriately treated in a timely manner. However, serious allergic reactions were reported rarely in association with NexoBrid in the post-marketing setting.

Post-Marketing Experience

Evaluation of data collected from the post marketing experience (spontaneous and solicited sources of information) did not identify any new and significant information and these data are in line with the safety profile of NexoBrid from the development programme.

Cumulatively since the IBD until 17 December 2021[20], 8 ADRs of allergic reactions (7 serious and 1 non-serious) were reported from spontaneous post-marketing sources in valid individual case safety reports. This represents a reporting rate of 0.09%, considering the total post-marketing patient exposure of 8,828 patients (refer to Section SV.1.2).

No anaphylactic reaction or serious allergic reactions occurred in any of the patients analysed in the retrospective, non-interventional PASS MW2013-06-01 (NexoPASS) completed in 2019 (N = 164).

Risk Factors and Risk Groups:

Allergic reactions to bromelain may occur in individuals allergic to pineapple or other members of the Bromeliaceae family, or those frequently exposed to bromelain (occupational inhalation exposure) (Kelly, 1996; Smolle et al, 2015).

Cross-sensitivity between bromelain and papain as well as latex proteins (known as latex-fruit syndrome), honeybee venom, and olive tree pollen has been reported in the literature (Brehler et al, 1997; Ebo et al, 2003; Basch et al, 2007; Casaer et al, 2008).

Since there are reports of occupational exposure to bromelain leading to sensitisation, the healthcare professionals preparing the final product may be at risk of hypersensitivity reactions.

Preventability:

The healthcare professionals mixing the powder with gel should avoid inhalation of the powder. Accidental eye and skin exposure must be avoided.

Patients with known hypersensitivity to pineapples or papain must not be treated with NexoBrid.

Refer to Part V.2 for a detailed description of the additional risk minimisation measures in place for this risk.

[20] The date represents the data lock point for the Addendum to Clinical Overview submitted for the second renewal of the marketing authorisation for NexoBrid, providing the most up-to-date post-marketing data for NexoBrid.

Impact on the Risk-Benefit Balance of the Product:

The impact is considered acceptable considering the use of NexoBrid in a hospital setting by experienced healthcare professionals.

Public Health Impact:

The anticipated frequency of serious allergic reactions, including anaphylaxis, in the post-marketing setting cannot be estimated based on available data.

Considering the low overall incidence of deep burn injuries and the eligibility criteria to NexoBrid treatment, the public health impact of this risk occurring in association with NexoBrid therapy is considered low.

SVII.3.1.5 Important Potential Risk 1: Severe Irritation

Potential Mechanism(s):

Not yet fully established for NexoBrid.

Proteolytic activity of bromelain on abraded skin may be the source of potential cutaneous irritation. Furthermore, bromelain was reported to function as a signalling molecule and activate protease-activated receptors. Activation of these receptors is a potential mechanism by which bromelain evokes itching (Reddy and Lerner, 2010).

Evidence Source(s) and Strength of Evidence:

This risk is based on the findings from the non-clinical studies within the development programme for NexoBrid, where severe irritation and pain were noted, following the application of NexoBrid to abraded skin of minipigs in the local tolerance studies. These findings suggest that there is a potential for reversible local reactions when NexoBrid is applied on intact skin and that contact with abraded skin could be irritating and painful.

No reports of any skin irritation following NexoBrid application were reported in the clinical development programme for NexoBrid.

Characterisation of the Risk:

Clinical Trials (Pooled Safety Analysis Set – Cohort 1 and Cohort 2 Studies; SIII.1)

'All TEAEs' were defined as those events that occurred in clinical studies after the start of treatment (NexoBrid, SOC, or placebo [gel vehicle]) and up to 3 months post wound closure of all treated wounds (i.e., acute phase) with the exception of Study MW2005-10-05, which was 1 month post wound closure.

Data from the 12- and 24-month follow-up in Study MW2010-03-02 (DETECT) are presented separately.

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Acute Phase (Up to 3 Months Post Wound Closure)

No reports of (severe) skin irritation following administration of NexoBrid were reported from the clinical development programme.

A moderate AE of rash was reported, following a second application of NexoBrid (Cohort 2). The aetiology of the rash is unknown and local irritation was hypothesised.

However, local hypersensitivity reaction could not have been ruled out and as such, this AE is reflected on in Section SVII.3.1.4.

12 Months and 24 Months Post Wound Closure (Study MW2010-03-02 [DETECT] Follow-Up Data)

No AEs of severe skin irritation were reported in the time period from 3 to 12 month as well as 12 to 24 months post wound closure.

Clinical Trials (Paediatric Population; SIII.2)

TEAEs were defined as adverse events that occurred after the start of treatment and up to 3 months post wound closure (i.e., acute phase). Additionally, the follow-up data for Study MW2012-01-01 (CIDS) are shown for the period from 12 weeks to 12 months post would closure.

Data are presented in this sub-section for the Study MW2012-01-01 (CIDS) and pooled populations (paediatric and adult) from the pooled studies (refer to SIII.2).

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

No reports of severe skin irritation following administration of NexoBrid were reported from study MW2012-01-01 (CIDS) within the Acute Phase (up to 12 weeks post wound closure) or in the time period from 12 weeks to 12 months post wound closure.

No reports of severe skin irritation associated with NexoBrid were reported in the paediatric pooled population or adult pooled population.

Impact on Quality of Life

It is not possible to estimate the impact on the individual patient, without further characterisation or this risk.

Post-Marketing Experience

Evaluation of data collected from the post marketing experience (spontaneous and solicited sources of information) did not identify any new and significant information and these data are in line with the safety profile of NexoBrid from the development programme.

Cumulatively since the IBD until 17 December 2021[21], 4 ADRs of skin irritation were reported from spontaneous post-marketing sources in valid individual case safety reports (3 cases reported in off-label use of NexoBrid for treatment of basal cell carcinoma, when the product is kept on the target area longer than for 4 hours used for eschar debridement). However, the severity of these events was not reported. Taking the conservative approach, this represents a reporting rate of 0.05%, considering the total post-marketing patient exposure of 8,828 patients (refer to Section SV.1.2).

No case of severe irritation was reported in the retrospective, non-interventional PASS MW2013-06-01 (NexoPASS), completed in 2019. No severe irritation was observed on

[21] The date represents the data lock point for the Addendum to Clinical Overview submitted for the second renewal of the marketing authorisation for NexoBrid, providing the most up-to-date post-marketing data for NexoBrid.

facial, perineal, or genital area in 14 patients (8.5% of 164 patients analysed) treated in these areas.

Risk Factors and Risk Groups:

Patients with abraded skin represent a risk group as these patients could be at increased risk of experiencing severe irritation.

Preventability:

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).

Refer to Part V.2 for a detailed description of the additional risk minimisation measures in place for this risk.

Impact on the Risk-Benefit Balance of the Product:

The impact of this potential risk on NexoBrid is acceptable in the light of anticipated treatment effects in burn patients.

Public Health Impact:

The anticipated frequency of severe irritation in the post-marketing setting cannot be estimated based on available data.

Considering the low overall incidence of deep burn injuries and the eligibility criteria to NexoBrid treatment, the public health impact of this risk potentially occurring in association with NexoBrid therapy is considered low.

SVII.3.1.6 Important Potential Risk 2: Increased Tendency to Bleeding

Potential Mechanism(s):

Bromelain consists of various closely-related proteinases, demonstrating anti-inflammatory, antithrombotic and fibrinolytic activities *in vitro* and *in vivo* (Pavan et al, 2012; Kaur et al, 2016).

Systemic exposure to bromelain may result in increased tendency to bleeding since bromelain was shown to inhibit blood platelet aggregation. *In-vitro* and *in-vivo* studies have shown that bromelain stimulates the conversion of plasminogen to plasmin, resulting in increased fibrinolysis by degrading fibrin (Taussig and Batkin, 1988; Lotz-Winter, 1990; Pavan et al, 2012). Preincubation of isolated human platelets *in vitro* with bromelain completely prevented the thrombin-induced platelet aggregation (Metzig et al, 1999).

In another *in-vitro* study, bromelain was shown to further inhibit platelet aggregation stimulated by adenosine diphosphate or epinephrine as well as by prostaglandin precursors in a dose-dependent manner, thus preventing adhesion of platelets to endothelial cells of blood vessels (Morita et al, 1979).

Evidence Source(s) and Strength of Evidence:

This risk is based on a theoretical possibility associated with topically administered NexoBrid and systemic effects of bromelain on blood coagulation, fibrinolysis, and platelet coagulation *in vivo* and *in vitro* (Pavan et al, 2012; Kaur et al, 2016).

Topical administration of NexoBrid was shown to produce a systemic exposure with highly variable serum levels (depending on the dose, % TBSA treated, and interindividual factors).

During the clinical development programme for NexoBrid and post-marketing experience, no indication of increased tendency to bleeding was noted.

Characterisation of the Risk:

Clinical Trials (Pooled Safety Analysis Set – Cohort 1 and Cohort 2 Studies; SIII.1)

'All TEAEs' were defined as those events that occurred in clinical studies after the start of treatment (NexoBrid, SOC, or placebo [gel vehicle]) and up to 3 months post wound closure of all treated wounds (i.e., acute phase) with the exception of Study MW2005-10-05, which was 1 month post wound closure.

Data from the 12- and 24-month follow-up in Study MW2010-03-02 (DETECT) are presented separately.

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Acute Phase (Up to 3 Months Post Wound Closure)

No indication of increased tendency to bleeding was noted in the clinical development programme.

Overall, in Cohort 2 studies, less than a sixth of patients in each group received blood transfusion(s) (16.4% of NexoBrid patients versus 14.1% of SOC patients). No blood transfusions were given before the start of treatment.

Blood transfusions were administered more often in the SOC group during and within 1 week after the eschar removal period but more often in the NexoBrid group later than 1 week after the eschar removal period.

The literature shows that oral administration of bromelain to healthy volunteers (780 mg/day for 10 days) showed no significant changes in blood coagulation parameters (i.e., aPTT) (Eckert et al, 1999).

Results of aPTT, which was assessed in Cohort 2 studies, showed that aPTT was comparable between groups at baseline (mean 30.5 s in NexoBrid and SOC versus 30.9 s in placebo treatment group; median 30.1 s in NexoBrid versus 30.2 s in SOC versus 29.7 s in placebo treatment group) and up to 24 hours after start of treatment (mean 31.7 s in NexoBrid versus 32.3 s in SOC versus 33.3 s in placebo treatment group; median 31.5 s in NexoBrid versus 31.0 s in SOC versus 31.2 s in placebo treatment group).

Blood transfusions were administered in Cohort 2 more often in the MW2004-11-02 study (20/100 [20%] NexoBrid patients versus 14/81 [17.3%] SOC patients) than in DETECT (9/77 [11.7%] NexoBrid patients versus 7/68 [10.3%] SOC patients).

12 Months and 24 Months Post Wound Closure (Study MW2010-03-02 [DETECT] Follow-Up Data)

No indication of increased tendency to bleeding was noted in the 3 to 12 months or 12 to 24 months post wound closure.

Clinical Trials (Paediatric Population; SIII.2)

TEAEs were defined as adverse events that occurred after the start of treatment and up to 3 months post wound closure (i.e., acute phase). Additionally, the follow-up data for Study MW2012-01-01 (CIDS) are shown for the period from 12 weeks to 12 months post would closure.

Data are presented in this sub-section for the Study MW2012-01-01 (CIDS) and pooled populations (paediatric and adult) from the pooled studies (refer to SIII.2).

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Study MW2012-01-01 (CIDS): Acute Phase (Up to 12 Weeks Post Wound Closure)

No indication of increased tendency to bleeding due to coagulation abnormalities was noted in study MW2112-01-01 (CIDS).

Seven patients (10.1%) in the NexoBrid group and 8 patients (11.4%) in the SOC group received blood transfusions during hospitalisation. Among these 15 patients, 5 patients treated with the SOC received blood transfusion during the eschar removal period, while none in the NexoBrid group. Three patients treated with NexoBrid and 1 treated with the SOC received a blood transfusion within a week after eschar removal period, and 4 patients treated with NexoBrid and 2 patients treated with the SOC received a blood transfusion later than 1 week after the eschar removal period.

Three (5.9%) patients in the NexoBrid treatment group (N = 51) had a shift from normal baseline international normalised ratio values to abnormal high values.

Three (3.7%) patients in the NexoBrid treatment group (N = 41) and 3 (13.0%) patients in the SOC treatment group had a shift from normal baseline to abnormal low aPTT.

One (2.4%) patient in the NexoBrid treatment group (N = 41) and 2 (8.7%) patients in the SOC treatment group had a shift from normal baseline to abnormal high aPTT.

Study MW2012-01-01 (CIDS): 12 Weeks to 12 Months Post Wound Closure Follow-Up Data

No indication of increased tendency to bleeding due to coagulation abnormalities was noted in the 12 weeks to 12 months post wound closure.

Pooled Populations (Paediatric and Adult)

No indication of increased tendency to bleeding due to coagulation abnormalities was noted in the paediatric or adult pooled populations.

Impact on Quality of Life

It is not possible to estimate the impact on the individual patient without further characterisation of this risk.

Post-Marketing Experience

Evaluation of data collected from the post marketing experience (spontaneous and solicited sources of information) did not identify any new and significant information and these data are in line with the safety profile of NexoBrid from the development programme.

Cumulatively since the IBD until 17 December 2021[22], 9 ADRs of haemorrhage were reported from spontaneous post-marketing sources in valid individual case safety reports. This represents a reporting rate of 0.10%, considering the total post-marketing patient exposure of 8,828 patients (refer to Section SV.1.2). None of the reported cases suggests increased tendency to bleeding, following administration of NexoBrid.

No increased tendency to bleeding was noted in patients analysed in the retrospective, non-interventional PASS MW2013-06-01 (NexoPASS) completed in 2019 (N = 164).

Risk Factors and Risk Groups:

Clinical pharmacokinetic data indicate that systemic exposure to NexoBrid can increase with the dose administered (either larger TBSA treated or repeated NexoBrid applications), therefore potentially increasing the risk of bleeding.

General risk factors for increased tendency to bleeding are coagulation abnormalities.

Preventability:

NexoBrid should not be applied to more than 15% TBSA (in paediatric patients aged 0 to 3 years to not more than 10% TBSA). Furthermore, a repeated application of NexoBrid on the same wound or in the patient where NexoBrid has already been used is not recommended.

NexoBrid should not be used in patients with uncontrolled disorders of coagulation. NexoBrid should be used with caution in patients under 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 of bleeding.

Refer to Part V.2 for a detailed description of the additional risk minimisation measures in place for this risk.

Impact on the Risk-Benefit Balance of the Product:

This potential risk may potentially have a significant impact on benefit-risk balance of NexoBrid. However, considering the low systemic exposure to NexoBrid when used according to the product information/risk minimisation measures in place, the anticipated benefits of the therapy outweigh this risk.

Public Health Impact:

The anticipated frequency of bleeding events in the post-marketing setting cannot be estimated based on available data.

Considering the low overall incidence of deep burn injuries and the eligibility criteria to NexoBrid treatment, the public health impact of this risk potentially occurring in association with NexoBrid therapy is considered low.

[22] The date represents the data lock point for the Addendum to Clinical Overview submitted for the second renewal of the marketing authorisation for NexoBrid, providing the most up-to-date post-marketing data for NexoBrid.

SVII.3.2 Presentation of Missing Information

SVII.3.2.1 Missing Information 1: Use in Pregnancy

Evidence Source:

Bromelain is systemically absorbed from burnt wound areas. However, no clinical data on pregnancies exposed to bromelain or NexoBrid are available.

Animal studies do not indicate any direct or indirect harmful effects on embryo-foetal development, but the relevance of these studies to human risk assessment is considered low due to increased sensitivity of rats and rabbits to systematically administered NexoBrid (refer to PART II: Module SII).

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

Anticipated Risk/Consequence of the Missing Information:

It is not possible to anticipate the potential impact on individual patient without further characterisation of this issue. However, NexoBrid could negatively impact the course of pregnancy or unborn child.

PART II: Module SVIII – Summary of Safety Concerns

Table 31: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Pain Pyrexia/hyperthermia Wound complications (including wound infections) Allergic reactions (including anaphylactic reaction)
Important potential risks	Severe irritation Increased tendency to bleeding
Missing information	Use in pregnancy

PART III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities beyond Adverse Reactions Reporting and Signal Detection:

- **Specific Adverse Reaction Follow-up Questionnaire**

The structured follow-up form is designed to optimise the collection of data needed for better understanding and characterisation of NexoBrid safety profile.

This form aims to collect detailed information about NexoBrid adverse event/reaction, respective patient and patient's relevant medical history including information about concomitant medication or laboratory testing.

The respective follow-up form is provided in Annex 4 of the RMP.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

PART V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 32: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Pain	**Routine Risk Communication:** SmPC sections 4.2, 4.8, and 5.3 PL sections 3 and 4 **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk:** Required pain management detailed in section 4.2 of the SmPC. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Restricted medical prescription
Pyrexia/hyperthermia	**Routine Risk Communication:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk:** Section 4.4 of the SmPC details additional monitoring of burn patients for rise in body temperature. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Restricted medical prescription
Wound complications (including wound infection)	**Routine Risk Communication:** SmPC sections 4.2, 4.4, and 4.8 PL sections 2, 3 and 4 **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk:** Detailed description of wound management and instructions for preventive measures against development of infection are included in sections 4.2 and 4.4 of the SmPC. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Restricted medical prescription

Safety Concern	Routine Risk Minimisation Activities
Allergic reactions (including anaphylactic reaction)	**Routine Risk Communication:** SmPC sections 4.3, 4.4, 4.8, and 6.6 PL sections 2 and 4 **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk:** Section 4.4 of the SmPC recommends additional monitoring of burn patients for signs of local or systemic allergic reactions. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Restricted medical prescription
Severe irritation	**Routine Risk Communication:** SmPC sections 4.2 and 5.3 **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk:** Section 4.2 of the SmPC recommends protection of abraded skin with sterile fatty ointment to prevent irritation. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Restricted medical prescription
Increased tendency to bleeding	**Routine Risk Communication:** SmPC sections 4.2, 4.4, and 4.5 PL section 2 **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk:** Section 4.4 of the SmPC provides recommendation for monitoring of signs of coagulation abnormalities in patients with coagulation disorders, low platelet counts, and increased risk of bleeding. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Restricted medical prescription
Use in pregnancy	**Routine Risk Communication:** SmPC section 4.6 PL section 2 **Other Routine Risk Minimisation Measures Beyond the Product Information:** Restricted medical prescription

PL = package leaflet; SmPC = summary of product characteristics

V.2 Additional Risk Minimisation Measures

Educational Materials

– Healthcare Professional Information Pack

Objectives:

The Healthcare Professional Information Pack is a step by step treatment guide.

Detailed instructions for NexoBrid use are divided into three sections: (1) before prescribing NexoBrid; (2) before applying NexoBrid and (3) after applying NexoBrid.

The key elements for the Healthcare Professional Information Pack are included in Annex 6.

– **List of Addressed Safety Concerns:**
  Pain
  Pyrexia/hyperthermia
  Wound complications (including wound infection)
  Allergic reactions (including anaphylactic reaction)
  Severe irritation
  Increased tendency to bleeding

Rationale for the Additional Risk Minimisation Activity:

The educational materials/training will ensure that all healthcare professionals working in specialised burn centres receive comprehensive step by step information how to use NexoBrid properly prior to the first administration.

Target Audience and Planned Distribution Path:

Education materials are distributed directly to the treating physicians in burn centres.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

The effectiveness of risk minimising intervention is assessed by routine pharmacovigilance activities, based on the analysis of spontaneously reported ADRs and other information available to the MAH at the time of Periodic Benefit-Risk Evaluation Report (PBRER) submission.

– Training for Healthcare Professionals

Objectives:

To give a guidance for treatment with NexoBrid, covering practical issues related to NexoBrid treatment referring to the following phases: wound preparation, pre-treatment soaking, NexoBrid application, NexoBrid removal, post removal soaking, options for wound management after end of treatment, and options for pain management.

– **List of Addressed Safety Concerns:**
Pain
Pyrexia/hyperthermia
Wound complications (including wound infection)
Allergic reactions (including anaphylactic reaction)
Severe irritation
Increased tendency to bleeding

Rationale for the Additional Risk Minimisation Activity:

The training will ensure that all healthcare professionals working in specialised burn centres receive comprehensive guidance on how to use NexoBrid properly and will clarify the main points in treatment.

Target Audience and Planned Distribution Path:

The training is conducted in the burn centres before starting to use NexoBrid. The training is given to the treating physicians in burn centres. The initial training is performed by MediWound trainers.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

The effectiveness of risk minimising intervention is assessed by routine pharmacovigilance activities, based on the analysis of spontaneously reported ADRs and other information available to the MAH at the time of PBRER submission.

V.3 Summary of Risk Minimisation Measures

Table 33: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pain	**Routine Risk Minimisation Measures:** – SmPC sections 4.2, 4.8, and 5.3 – PL sections 3 and 4 Recommendation for pain management in section 4.2 of the SmPC and section 3 of PL. Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Pyrexia/hyperthermia	**Routine Risk Minimisation Measures:** – SmPC sections 4.4 and 4.8 – PL sections 2 and 4 Section 4.4 of the SmPC recommends additional monitoring of burn patients for rise in body temperature and signs of local and systemic inflammatory and infectious processes. Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Wound complications (including wound infections)	**Routine Risk Minimisation Measures:** – SmPC sections 4.2, 4.4, and 4.8 – PL sections 2, 3, and 4 Detailed description of wound management and instructions for preventive measures against development of infection are included in sections 4.2 and 4.4 of the SmPC and section 3 of the PL. Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	– Training	
Allergic reactions (including anaphylactic reaction)	**Routine Risk Minimisation Measures:** – SmPC section 4.3, 4.4, 4.8, and 6.6 – PL sections 2 and 4 Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Severe irritation	**Routine Risk Minimisation Measures:** – SmPC sections 4.2 and 5.3 Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Increased tendency to bleeding	**Routine Risk Minimisation Measures:** – SmPC sections 4.2, 4.4, and 4.5 – PL section 2 Section 4.4 of the SmPC recommendation for monitoring of signs of coagulation abnormalities in patients with coagulation disorders, low platelet counts, and increased risk of bleeding. Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Use in pregnancy	**Routine Risk Minimisation Measures:** – SmPC section 4.6 – PL section 2 Restricted medical prescription	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None

PL = package leaflet; SmPC = summary of product characteristics

PART VI: Summary of the Risk Management Plan

Summary of risk management plan for NexoBrid (concentrate of proteolytic enzymes enriched in bromelain)

This is a summary of the risk management plan (RMP) for NexoBrid. The RMP details important risks of NexoBrid, how these risks can be minimised, and how more information will be obtained about NexoBrid's risks and uncertainties (missing information).

NexoBrid's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how NexoBrid should be used.

This summary of the RMP for NexoBrid should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of NexoBrid's RMP.

I. The medicine and what it is used for

NexoBrid is authorised for removal of eschar in patients with deep partial- and full-thickness thermal burns (see SmPC for the full indication). It contains concentrate of proteolytic enzymes enriched in bromelain as the active substance and it is given by topical route of administration.

Further information about the evaluation of NexoBrid's benefits can be found in NexoBrid's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of NexoBrid, together with measures to minimise such risks and the proposed studies for learning more about NexoBrid's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of NexoBrid, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of NexoBrid is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of NexoBrid are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of NexoBrid. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Pain Pyrexia/hyperthermia Wound complications (including wound infections) Allergic reactions (including anaphylactic reaction)
Important potential risks	Severe irritation Increased tendency to bleeding
Missing information	Use in pregnancy

II.B Summary of important risks

Identified risk: Pain	
Evidence for linking the risk to the medicine	This risk is based on the findings from the non-clinical as well as clinical part of the development programme for NexoBrid, where local pain was identified as an accompanying symptom of enzymatic debridement.
Risk factors and risk groups	No risk groups or specific risk factors have been identified for the events of pain associated with NexoBrid enzymatic debridement.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.8, and 5.3 PL sections 3 and 4 Recommendation for pain management in section 4.2 of the SmPC and section 3 of PL. Restricted medical prescription

	Additional risk minimisation measures: Healthcare Professional Information Pack Training

Identified risk: Pyrexia/hyperthermia	
Evidence for linking the risk to the medicine	Pyrexia/hyperthermia were the most commonly reported adverse reactions associated with the use of NexoBrid in clinical trials. The frequency of the pyrexia/hyperthermia decreased when NexoBrid was used in a regimen, introducing antibacterial soaking of the treatment area before and after NexoBrid application and administration of preventive analgesia.
Risk factors and risk groups	There are several different possible risk factors for pyrexia/hyperthermia in burn patients, such as infection or contaminated wound.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Section 4.4 of the SmPC recommends additional monitoring of burn patients for rise in body temperature and signs of local and systemic inflammatory and infectious processes. Restricted medical prescription Additional risk minimisation measures: Healthcare Professional Information Pack Training

Identified risk: Wound complications (including wound infections)	
Evidence for linking the risk to the medicine	Various wound complications, including a delay in time to complete wound closure (in certain cases linked to a selected wound-care strategy) and wound infections, were reported in early clinical development programme for NexoBrid. The implementation of preventive measures later in the programme led to a decrease in the incidence of general wound infections. However, wound complications (including wound infections) remain an important risk associated with NexoBrid treatment.

Risk factors and risk groups	Patients with burn area greater than 30% TBSA or old, contaminated burns are at increased risk of wound complications, same as burn patients with full-thickness wounds and deep burns that can spontaneously epithelise and are not autografted immediately after debridement for time to complete wound closure. Immunosuppressed patients are in general at higher risk of wound infections and sepsis.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.4, and 4.8 PL sections 2, 3, and 4 Detailed description of wound management and instructions for preventive measures against development of infection are included in sections 4.2 and 4.4 of the SmPC and section 3 of the PL. Restricted medical prescription <u>Additional risk minimisation measures:</u> Healthcare Professional Information Pack Training

Identified risk: Allergic reactions (including anaphylactic reaction)	
Evidence for linking the risk to the medicine	Allergic reactions associated with NexoBrid application, including infrequent events of anaphylactic reaction, were reported from the post-marketing experience with NexoBrid. Allergic reactions to bromelain have been reported in the literature, mostly related to cases of airway sensitisation resulting from occupational exposure or general pineapple allergy.
Risk factors and risk groups	Allergic reactions to bromelain may occur in individuals allergic to pineapple or other members of the Bromeliaceae family, or those frequently exposed to bromelain (occupational inhalation exposure). Cross-sensitivity between bromelain and papain as well as latex proteins (known as latex fruit syndrome), honeybee venom, and olive tree pollen has been reported in the literature. Since there are reports of occupational exposure to bromelain leading to sensitisation, the healthcare professionals preparing the final product may be at risk of hypersensitivity reactions.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3, 4.4, 4.8, and 6.6 PL sections 2 and 4 Restricted medical prescription Additional risk minimisation measures: Healthcare Professional Information Pack Training

Potential risk: Severe irritation	
Evidence for linking the risk to the medicine	This risk is based on the findings from the non-clinical studies within the development programme for NexoBrid, where severe irritation and pain were noted, following the application of NexoBrid to abraded skin of minipigs in the local tolerance studies. These findings suggest that there is a potential for reversible local reactions when NexoBrid is applied on intact skin and that contact with abraded skin could be irritating and painful. No reports of any skin irritation following NexoBrid application were reported in the clinical development programme for NexoBrid.
Risk factors and risk groups	Patients with abraded skin represent a risk group as these patients could be at increased risk of experiencing severe irritation.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 5.3 Restricted medical prescription Additional risk minimisation measures: Healthcare Professional Information Pack Training

Potential risk: Increased tendency to bleeding	
Evidence for linking the risk to the medicine	This risk is based on a theoretical possibility associated with topical NexoBrid and systemic effects of bromelain on blood coagulation, fibrinolysis, and platelet coagulation *in vivo* and *in vitro*. Topical administration of NexoBrid was shown to produce a systemic exposure with highly variable

	serum levels (depending on the dose, % TBSA treated, and interindividual factors). During the clinical development programme for NexoBrid and post-marketing experience, no indication of increased tendency to bleeding was noted.
Risk factors and risk groups	Clinical pharmacokinetic data indicate that systemic exposure to NexoBrid can increase with the dose administered (either larger TBSA treated or repeated NexoBrid applications), therefore potentially increasing the risk of bleeding. General risk factors for increased tendency to bleeding are coagulation abnormalities. NexoBrid should not be used in patients with uncontrolled coagulation disorders. NexoBrid should be used with caution in patients under 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.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.5 PL section 2 Section 4.4 of the SmPC recommendation for monitoring of signs of coagulation abnormalities in patients with coagulation disorders, low platelet counts, and increased risk of bleeding. Restricted medical prescription Additional risk minimisation measures: Healthcare Professional Information Pack Training

Missing information: Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Restricted medical prescription

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of NexoBrid.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for NexoBrid.

PART VII: Annexes

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

MediWound

FOLLOW-UP FORM

Requested by:	Date:

REPORTER *(please fill in missing information)*

Last name:

First:

Address:

Email address:

Profession: Physician

PATIENT *(please fill in missing information)*

Initials: Gender: ☐ Male ☐ Female Age: Weight: Height: Ethnicity:	Relevant medical history (if any):

NEXOBRID TREATMENT *(please fill in missing information)*

Suspect medicinal product	Dose administered (g)	Route of administration	Administration Date	Total body surface area (TBSA), on which NexoBrid was applied	Duration of application
NexoBrid - first application				Click or tap here to enter text.	
NexoBrid - second application					

NexoBrid - third application					

- TYPE OF BURN:

  ☐Thermal burn

  ☐Electrical burn

  ☐Chemical burn

  ☐Other – please specify:

- %TBSA AFFECTED BY ALL BURNs THE PATIENT SUFFERED (not only those treated with NexoBrid). Please specify anatomical locations:

- WAS THE BURN TREATED BY NEXOBRID DEEP OR SUPERFICIAL?

  ☐Superficial

  ☐Deep

- PARTS OF BODY ON WHICH NEXOBRID WAS APPLIED (SELECT ALL APPLICABLE):

  ☐Face

  ☐Head

  ☐Body (torso)

  ☐Extremities (both forearms, hands, fingers and ankles)

  ☐Perineal and genital area

- WAS NEXOBIRD USED WITH MORE THAN ONE APPLICATION IN THIS PATIENT?

  ☐No

  ☐Yes – please specify:

  - What was the reason for repeated use? *(e.g. >15% TBSA)*:

  - Was the application repeated on the same burn area?

  ☐No

  ☐Yes

- DID PATIENT DEVELOP ANY ADVERSE DRUG REACTION AFTER NEXOBRID APPLICATION?

  ☐ yes ☐ no

  If yes, please specify in section ADVERSE REACTION(S) in the next page

ADVERSE REACTION(S)

Adverse reaction	Start date	End date	Serious Yes/No* (if serious, please select seriousness criterion/criteria)	Outcome (Resolved/ongoing/resolved with sequelae/other (please specify)/unknown)	Causality (was the AE related to NexoBrid?) Yes/No

OTHER MEDICATION/THERAPY *(please complete information about relevant medication/therapy)*

Other suspected medicinal product	Daily dose	Route of administration	Start date	End date	Indication
-					
-					
-					
Concomitant medication	**Daily dose**	**Route of administration**	**Start date**	**End date**	**Indication**

Therapy used to treat ADR	Daily dose	Route of administration	Start date	End date	Indication

*Serious AEs should fulfill one of the following criteria: patient's death; life-threatening adverse reaction; adverse reaction results in inpatient hospitalization or prolongation of existing hospitalization; adverse reaction caused persistent or significant disability or incapacity; adverse reaction caused congenital anomaly/birth defect; adverse reaction is medically important

OTHER RELEVANT INFORMATION
Recorded by: **Date:** **Signature:**

Annex 6 - Details of Proposed Additional Risk Minimisation Measures

Approved Key Messages of the Additional Risk Minimisation Measures

Prior to launch in each Member State, the marketing authorisation holder (MAH) shall agree the content and format of the educational programme with the National Competent Authority. The MAH should ensure that, at launch, all healthcare professionals in specialist burn centres who are expected to use and/or prescribe NexoBrid receive a specific training and are provided with an educational pack.

The MAH should undertake a controlled distribution of NexoBrid to ensure that the product is not available for use at a centre until at least one surgeon at the centre has received formal training in the use of NexoBrid. This is in addition to the educational material which all potential users should receive.

The educational pack should contain the following:

- Summary of Product Characteristics and Package Leaflet
- Healthcare Professional Information Pack.

The **Healthcare Professional Information Pack** should be a step-by-step treatment guide that includes information on the following key elements:

- Before prescribing NexoBrid
    - The limitation of the total area than can be treated to 15% TBSA (or 10% TBSA in paediatric patients aged 0 to 3 years)
    - The risk of allergic reaction and of cross reactivity and the contraindication in patients allergic to pineapple and papain or to previous application of the product
    - The risk of increased mortality in patients with cardiopulmonary diseases
- Before applying NexoBrid
    - The need for pain management
    - The need for wound cleansing and preparation before treatment with
        - Application of a dressing soaked with an antibacterial solution for two hours before NexoBrid application
        - Protection of surrounding skin areas
    - The method of preparation of NexoBrid and of its application to wound area
- After applying NexoBrid
    - The removal of NexoBrid and of dissolved eschar
    - The wound assessment and the warning against any repeat treatment
    - The wound management after NexoBrid treatment with
        - Application of a dressing soaked with an antibacterial solution for two hours
        - Performance of grafting procedures as soon as possible after debridement

- The fact that NexoBrid may cause an allergic reaction, an increased tendency to bleed and severe local irritation and that patients should be monitored for signs and symptoms of these
- The fact that patients should be monitored for signs and symptoms of wound and systemic infections