Triskel Integrated Services SA

Summary of the Risk Management Plan (RMP) for NexoBrid, poudre et gel pour gel (concentrate of proteolytic enzymes enriched in bromelain)

Marketing Authorisation Holder: Triskel Integrated Services

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of NexoBrid is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the ”Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of NexoBrid in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Triskel Integrated Services is fully responsible for the accuracy and correctness of the content of the published summary RMP of NexoBrid.

Summary of the Risk Management Plan (RMP) 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 adults 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	Long-term (at least 2 years) cosmetic and functional outcomes Use in pregnancy Development of anti-NexoBrid antibodies

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 groups were identified to be at unique risk. There are no known risk factors.
Risk minimisation measures	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
Additional pharmacovigilance activities	Study MW2010-03-02 See section II.C of this summary for an overview of the post-authorisation development plan.

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 which included recommended preventive analgesia as routinely practiced for extensive dressing changes in burn patients as well as antibacterial soaking of the treatment area before and after NexoBrid application.
Risk factors and risk groups	There are several different possible risk factors for pyrexia/hyperthermia in burn patients, such as infection or contaminated wound. Handling (including surgery, debridement and dressing change) of contaminated eschar may release tissue maceration, catabolic and bacterial products with temperature elevation with or without bacteraemia.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> 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
Additional pharmacovigilance activities	Study MW2010-03-02 See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk: Wound complications (including wound infections)	
Evidence for linking the risk to the medicine	Wound infection represented the majority of wound complications observed in NexoBrid clinical development programme. The incidence of wound infection was similar across studies. In Study MW2004-11-02, time to complete wound closure (TTCWC) was 31.3 days for NexoBrid treatment arm as compared to 27.4 days for standard of care (SoC) arm. However, TTCWC was similar between NexoBrid and SoC treatment arms for wounds that are regularly autografted (full-thickness burn population), based on post hoc analyses.
Risk factors and risk groups	Patients with greater than 30% TBSA burns 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 TTCWC.
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
Additional pharmacovigilance activities	Study MW2010-03-02 See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk: Allergic reactions (including anaphylactic reaction)	
Evidence for linking the risk to the medicine	Allergic reactions to bromelain have been reported in the literature, mostly related to cases of airway sensitisation resulting from occupational exposure. Allergic reactions associated with NexoBrid application, including 2 events of anaphylactic reaction, were reported from the post-marketing experience with NexoBrid.
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 reaction.
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
Additional pharmacovigilance activities	Study MW2010-03-02 See section II.C of this summary for an overview of the post-authorisation development plan.

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. In clinical trials with NexoBrid, there were no reports of any irritation following NexoBrid application. NexoBrid was used for treatment of facial/perineal/genital burns in 14/164 patients (8.5%) in NexoPASS study. No severe irritation case was observed on facial/perineal/genital area nor on other body areas.
Risk factors and risk groups	The potential risk group represent patients with abraded skin as these patients could be in higher risk of 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
Additional pharmacovigilance activities	Study MW2010-03-02 See section II.C of this summary for an overview of the post-authorisation development plan.

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. Neither the clinical development programme nor post-authorisation experience indicate adverse reactions attributable to increased tendency to bleeding when used locally for enzymatic debridement.
Risk factors and risk groups	Clinical pharmacokinetic data indicate that systemic exposure to NexoBrid/bromelain can increase with the dose administered (either larger TBSA treated or repeated NexoBrid applications). General risk factors for increased tendency to bleeding are coagulation abnormalities. Caution should be exercised in using NexoBrid in patients with coagulation disorders, low platelet counts and increased risk of bleeding from other causes, such as peptic ulcers and sepsis. Patients treated with anticoagulants/blood thinning agents can be at higher risk of increased tendency to bleeding due to a potentially additive effect.
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
Additional pharmacovigilance activities	Study MW2010-03-02 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term (at least 2 years) cosmetic and functional outcomes	
Risk minimisation measures	Routine risk minimisation measures: Restricted medical prescription
Additional pharmacovigilance activities	Study MW2010-03-02 See section II.C of this summary for an overview of the post-authorisation development plan.

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

Missing information: Development of anti-NexoBrid antibodies	
Risk minimisation measures	None
Additional pharmacovigilance activities	Study MW2010-03-02 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

The following study is condition of the marketing authorisation:

Study short name

DETECT study (MW2010-03-02)

Purpose of the study

Evaluation of the efficacy and safety of NexoBrid in the treatment of thermal burns as compared with the standard of care. Safety concerns covered are Pain, Pyrexia/hyperthermia, Wound complications (including wound infections), Severe irritation, Effects of systemic exposure to NexoBrid and Long-term (at least 2 years) cosmetic and functional outcomes.

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

Not applicable