Refixia® - Powder and solvent for solution for injection

Summary of the risk management plan (RMP) for Refixia® (nonacog beta pegol)

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1 Summary of the risk management plan (RMP) for Refixia® (Nonacog beta pegol)

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 minimize them. The RMP summary of Refixia® 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“ 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 Refixia® in Switzerland is the „Arzneimittelinformation“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Novo Nordisk Pharma AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Refixia®.

2 Overview of disease epidemiology

Haemophilia B is a rare bleeding disorder that predominately affects males and causes patients to have a longer bleeding time. In people with haemophilia B, the protein called “factor IX” (FIX in short), which helps the blood to form clots when there is bleeding, is either missing in the blood or does not work properly. Therefore, these patients cannot form a proper blood clot and may have big bruises and bleeding in muscles and joints, causing pain, stiffness and swelling.

Haemophilia B is an inherited disease that most commonly is passed down from a parent to a child. About 1 in 25,000 boys are born with haemophilia B. 28,430 persons have been diagnosed with haemophilia B worldwide. At least 86% of them are men and at least 3% are women; the sex of the remaining people (11%) is unknown.

3 Summary of treatment benefits

Nonacog beta pegol is a version of human FIX which enables proper clotting of blood in individuals with haemophilia B who are missing FIX in their blood.

The ability of nonacog beta pegol to prevent and treat bleeds in people with haemophilia B has been demonstrated in a number of studies:

1. **First study in humans:** 16 patients were given one dose of nonacog beta pegol, which lasted 5 times longer than other marketed FIX products available at the time the trial was conducted.

2. **Prevention and treatment of bleeds**: 74 patients were treated in one study, either to prevent bleeds for 12 months or to treat bleeds for 6 months. A total of 92.2% of the bleeds were successfully stopped in this study.

3. **Treatment during major surgery**: 15 patients were successfully treated with nonacog beta pegol in connection with major surgery (16 surgeries).

4. **Treatment for longer time**: Patients from the studies in bullets 2 and 3 were treated for a longer period and nonacog beta pegol successfully treated 94.6% of the bleeds.

5. **Treatment in children**: 24 children below 12 years of age have been treated to prevent bleeds for 1 year. So far nonacog beta pegol successfully treated 92.9% of the bleeds and the children have had about one bleeding per year.

In the studies above, the patients had previously been treated with another FIX product. The overall success rate for treatment of bleeds in these studies was 93%.

In addition to these studies, one study is currently ongoing where patients who were not previously treated with a FIX product are included.

4 Unknowns relating to treatment benefits

Elderly people and people with mild haemophilia B are among the groups that have not been treated with nonacog beta pegol. The studies mainly included white adult men. People of other race/ethnicity or age are not expected to respond differently to nonacog beta pegol. A study in small children not previously treated with a FIX is ongoing.

5 Summary of safety concerns

The known and possible safety concerns are listed in Table 5.1, Table 5.2 and Table 5.3.

5.1 Known risks

Risk	What is known	Preventability

Allergic reactions (Allergic/hypersensitivity reactions)	The body could react against nonacog beta pegol with an allergic reaction. Allergic reactions may include rash, tightness of the chest, wheezing, low blood pressure, and may occasionally be life-threatening.	It is not known if an allergic reaction will develop. However, if allergic reactions related to nonacog beta pegol occur, the treatment should be stopped immediately. The first injections should be administered in a medical clinic or in the presence of healthcare professionals where proper medical care for allergic reactions can be provided.
The body may produce antibodies against nonacog beta pegol (FIX inhibitors)	If this happens, the body will react against nonacog beta pegol. This means that immunity to nonacog beta pegol can develop and nonacog beta pegol may not work properly. The risk of developing antibodies is higher in patients not previously treated with FIX than previously treated patients.	It is not known how antibody production can be prevented.

Abbreviations: FIX = factor IX.

5.2 Potential risks

Risk	What is known (including reason why it is considered a potential risk)
Blood clots (Thromboembolic events)	When treating with a blood coagulation factor like nonacog beta pegol, there is a risk that blood clots are formed. So far no blood clots have been seen when people have been treated with nonacog beta pegol.
Kidney disease when giving nonacog beta pegol as ITI therapy (Nephrotic syndrome following ITI)	If nonacog beta pegol is given as ITI therapy to people with haemophilia B and antibodies, there is a risk that the kidneys get damaged. This has so far not been seen since nonacog beta pegol has not been used for ITI therapy.
No treatment given or too little nonacog beta pegol given due to difficulties in measuring the correct FIX levels in the blood (Inadequate treatment due to assay overestimation of FIX activity)	Since there are different types of methods to measure FIX levels, the results could vary. This could result in the physician thinking the patient has enough FIX and no treatment is given, when it is actually needed. This could result in the patient starting to bleed or an existing bleed not being stopped.

Note: ITI (immune tolerance induction) is when patients with inhibitors are given higher doses of nonacog beta pegol more often than recommended.

Abbreviations: FIX = factor IX; ITI = immune tolerance induction.

5.3 Information that is not currently available

Risk	What is known
Use in people not treated with FIX before	One study is ongoing where children, who have not been treated with FIX products before are receiving nonacog beta pegol. Only limited information is available at this time.

Use in elderly people	No people over 65 years have been included in studies with nonacog beta pegol. Therefore, it is not known if nonacog beta pegol is effective or safe in this group of people.
Use in people with mild haemophilia B and moderate haemophilia B with FIX activity >2% - 5%	People with mild haemophilia B and some patients with moderate haemophilia B (whose FIX activity is above 2% and up to 5%) have not been treated with nonacog beta pegol so far. Therefore, it is not known if nonacog beta pegol is effective or safe in this group of people.
Use in females with haemophilia B, including pregnant or breastfeeding women	No women have been treated with nonacog beta pegol so far, as this disease is rare in women. Nonacog beta pegol should only be used in pregnant and breastfeeding women if clearly needed.
Patients with a high amount of HIV	Only a few people with a high amount of HIV have been treated with nonacog beta pegol so far. Therefore, it is not known if nonacog beta pegol is effective or safe in this group of people.
Use in people with kidney problems	People with kidney problems have not been treated with nonacog beta pegol so far. Therefore, it is not known if nonacog beta pegol is effective or safe in this group of people.
Use in people with liver problems	There is limited experience in people with liver problems. Therefore, it is not known if nonacog beta pegol is effective or safe in this group of people.
Use in people who have had antibodies against FIX	No people, with previous experience of antibodies against FIX, have been treated with nonacog beta pegol so far. Therefore, it is not known if nonacog beta pegol is effective or safe in this group of people.
Use in people who have had blood clots before	Only one person who has had blood clots before has been treated with nonacog beta pegol so far. Therefore, it is not known if nonacog beta pegol is effective or safe in this group of people.
Use for ITI treatment	No people with FIX antibodies have been treated with nonacog beta pegol as ITI treatment. Therefore, it is not known if nonacog beta pegol is effective or safe in this group of people.

Note: ITI (immune tolerance induction) is when patients with inhibitors are given higher doses of nonacog beta pegol more often than recommended.

Abbreviations: FIX = factor IX; HIV = human immunodeficiency virus; ITI = immune tolerance induction.

6 Summary of risk minimisation measures by safety concern

Safety concerns presented in the previous tables are addressed in the leaflet included in each package of nonacog beta pegol. Novo Nordisk A/S concludes that this is sufficient and no extra measures are needed.

7 Planned post-authorisation development plan

No further post-authorisation efficacy studies are needed for nonacog beta pegol.

8 Summary of changes to the risk management plan over time

Not applicable, as this is the first Edition of the RMP being submitted.