PART VI.2 ELEMENTS FOR A PUBLIC SUMMARY

Part VI.2.1 Overview of disease epidemiology

Idarucizumab (Praxbind) is a specific reversal agent for dabigatran and is indicated in adult patients treated with dabigatran etexilate (Pradaxa) when rapid reversal of its anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures as well as in life-threatening or uncontrolled bleeding. Epidemiological data is currently only available for bleeding events and not for emergency surgeries/procedures.

The incidence rate of major bleeding events in observational studies ranges between 2.1 and 4.3 per 100 PY in the Pradaxa SPAF indication depending on country and the respective dataset. The results for major bleeding events in observational studies are in general concordant with the trial results of the RE-LY study. No observational data is currently available for life-threatening bleeding events, bleeding events in other Pradaxa indications, and not for the incidence of emergency surgeries/procedures.

In RE-LY, the incidence rates for life-threatening bleeding events were 1.27 per 100 PY for dabigatran etexilate 110 mg bid and 1.52 per 100 PY for dabigatran etexilate 150 mg bid. The incidence rate of emergency surgeries/procedures requiring dabigatran interruption in the RE-LY trial was 1.5 per 100 PY for dabigatran etexilate 110 mg bid and 1.76 per 100 PY for dabigatran etexilate 150 mg bid.

Part VI.2.2 Summary of treatment benefits

In 3 Phase I studies in subjects and an ongoing Phase III study in patients (interim analysis), 5 g of idarucizumab completely reversed the blood thinning (anticoagulant) effect of dabigatran. This was established using several different blood clotting (coagulation) tests and corroborated by simultaneously measuring the disappearance of unbound sum dabigatran. An immediate, complete, and sustained effect was demonstrated in subjects, in the elderly, in renally impaired subjects, and in patients with life-threatening or urgent conditions that required immediate intervention. This reversal was also demonstrated to be dose-dependent and dependent on the amount of dabigatran in the patient. A dose of 5 g of idarucizumab was calculated to be sufficient for full reversal of the dabigatran blood thinning effect in 99% of patients, based on dabigatran plasma concentrations observed in the RE-LY trial. A massive amount of dabigatran, as could occur in cases of Pradaxa overdosage, may also be reversed by the proposed clinical dose of 5 g.

Part VI.2.3 Unknowns relating to treatment benefits

Idarucizumab was not investigated in children (age younger than 18 years). Idarucizumab has not been studied in pregnant/breast-feeding women. Experience with re-exposure to idarucizumab is limited.

Part VI.2.4 Summary of the safety concerns

PVI.Table 5 Important identified risks

Risk	What is known	Preventability
None		

PVI.Table 6 Important potential risks

Risk	What is known (incl. reason why it is considered a potential risk)
Ability of idarucizumab to induce an immune response (immunogenicity)	To address immunogenicity of idarucizumab (i.e. the ability of idarucizumab to induce an immune response), antibody formation against idarucizumab as well as dabigatran was analysed throughout the clinical Phase I studies, including a 3-months follow-up period. No apparent correlation of antibody development to frequency of adverse events was observed in any of the 3 Phase I trials. Data on anti-drug antibodies (ADAs) were available for 47 patients from the clinical Phase III trial. No adverse events indicating potential risks that could have been caused by ADAs were observed in any of the patients.
Allergic reactions (hypersensitivity)	Allergic reactions are currently not known to be associated with the use of idarucizumab or its excipients. No such adverse events were observed in the clinical Phase III trial.
Blood clotting events (thrombotic events)	The target population is adult patients being treated with dabigatran etexilate in order to prevent the formation of blood clots. Idarucizumab reverses the blood thinning (anticoagulant) effect of dabigatran etexilate. Therefore, due to the underlying condition of the patient and the reversal effect of idarucizumab, blood clots might form in patients receiving idarucizumab. Five patients developed thrombotic events; in one patient the events occurred within 2 days of idarucizumab treatment.

PVI.Table 7 Missing information

Risk	What is known
Children (paediatric patients)	Idarucizumab has not been studied in patients younger than 18 years. A paediatric investigational plan including a deferral has been granted by EMA.
Pregnancy/breast-feeding	Idarucizumab has not been studied in pregnant or breast-feeding women. Reproductive and developmental toxicity studies have not been performed, given the nature and the intended clinical use of the medicinal product. Idarucizumab may be used during pregnancy, if the clinical benefit outweighs the potential risks. It is unknown if idarucizumab is excreted in human milk.
Re-exposure to idarucizumab	In subjects, the frequencies of pre-existing anti-idarucizumab antibodies with cross-reactivity to idarucizumab were low and idarucizumab was well tolerated in subjects with pre-existing antibodies. Further, in subjects, the frequencies of treatment-emergent anti-idarucizumab antibodies were low; therefore it can be concluded that idarucizumab has a low immunogenic potential. Data on re-exposure in patients is available for 2 patients who experienced re-bleeds; in both patients the clotting times normalised and the bleeding stopped after the second 5 g dose.

Part VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for idarucizumab can be found in the idarucizumab's EPAR page.

This medicine has no additional risk minimisation measures.

Part VI.2.6 Planned post-authorisation development plan

PVI.Table 8 List of studies in post-authorisation development plan

Study/activity (incl. study number)	Objectives	Safety concerns/efficacy issue addressed	Status	Planned submission date of (interim and) final results
Trial 1321.3 - A Phase III case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures	To evaluate the reversal of the anticoagulant effects of dabigatran by i.v. administration of 5.0 g idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures	Immunogenicity, hypersensitivity, thrombotic events	Started	Final report Q1 2017

Studies which are a condition of the marketing authorisation:

None of the above studies is a condition of the marketing authorisation.

Part VI.2.7 Summary of changes to the RMP over time

Not applicable as this is the first RMP for idarucizumab.