Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report for the non-interventional imposed PASS final report for the medicinal product(s) containing the active substance intravenous aprotinin and concerned by the PASS final report, the scientific conclusions are as follows:

The MAH submitted the final study report version 1.0 dated 08-JAN-2021, updated on 31-MAY-2021, for a category 1 non-interventional PASS imposed as a condition to the MA of aprotinin. The Nordic Aprotinin Patient Registry (NAPaR), is a multicentre, non-interventional study with active surveillance via patient exposure registry aimed, among other outcomes, to measure the incidence of safety outcomes associated with the use of aprotinin in real-life.

The NAPaR results are essentially in accordance with the known safety profile of aprotinin when used in the approved indication, and updates to the product information are proposed to reflect these results. Nonetheless, the extensive off-label use (75% of aprotinin use in other procedures than iCABG, and 70% of use in low or moderate bleeding risk) observed despite restricted distribution in a registry are of concern. The lack of knowledge (perceived medical need in high-risk patients undergoing cardiac surgeries or patients undergoing complex high-risk cardiac surgeries) has been offered as a possible explanation for the non-adherence to the product information.

Given the concerns raised by the extensive off-label use of aprotinin, the PRAC Rapporteur considers necessary to minimize the risk and inform HCP that the benefit/risk balance of aprotinin has not been established for any indication outside the authorized indication. ~~An updated~~ Educational Material should be distributed which includes key elements on the risks associated with the use of aprotinin, and information about uncertainties on the role of aprotinin in risks of mortality and severe haemorrhage in off-label use. The purpose of the Education Materials is to ensure that the prescription of aprotinin is according to the authorised indication. A cover letter to accompany the educational material is proposed but should be agreed with national agencies. Effectiveness assessment of RMMs should be included in the RMP update and results should be discussed in the PSUR reports.

Therefore, in view of available data regarding the PASS final study report, the PRAC Rapporteur considered that an updated educational programme is required with aim at reducing off-label use of intravenous aprotinin and educating healthcare professionals about its key risks and how to ensure adequate anticoagulation during its use. Consequent update to the risk management plan is warranted. Updates to the product information are recommended.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for the results of the study for the medicinal product(s) containing the active substance intravenous aprotinin and concerned by the PASS final report, the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) mentioned above is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of the products concerned by this PASS final report should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Summary of Product Characteristics (new text **underlined and in bold,** deleted text ~~strike through~~)

4.2. Posology and method of administration

Posology:

An appropriate aprotinin-specific IgG antibody test may be considered **if available** before administration of aprotinin (see section 4.3).

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4.4 Special warnings and precautions for use

Laboratory monitoring of anticoagulation during cardiopulmonary bypass

Aprotinin is not a heparin-sparing agent and it is important that adequate anticoagulation with heparin be maintained during aprotinin-therapy. ~~Elevations in the partial thromboplastin time (PTT) and celite Activated Clotting Time (Celite ACT) are expected in aprotinin-treated patients during surgery, and in the hours after surgery. Therefore, the partial thromboplastin time (PTT) should not be used to maintain adequate anticoagulation with heparin. In patients undergoing cardiopulmonary bypass with aprotinin therapy, one of three methods is recommended to maintain adequate anticoagulation: Activated Clotting Time (ACT), Fixed Heparin Dosing, or Heparin Titration (see below). If activated clotting time (ACT) is used to maintain adequate anticoagulation, a minimal celite ACT of 750 seconds or kaolin ACT of 480 seconds, independent of the effects of haemodilution and hypothermia, is recommended in the presence of aprotinin.~~

~~*Additional note on use with extracorporeal circulation*~~

~~In patients undergoing cardiopulmonary bypass with aprotinin therapy, one of the following methods is recommended to maintain adequate anticoagulation:~~

~~* Activated Clotting Time (ACT)~~

~~An ACT is not a standardized coagulation test, and different formulations of the assay are affected differently by the presence of aprotinin. The test is further influenced by variable dilution effects and the temperature experienced during cardiopulmonary bypass. It has been observed that kaolin-based ACTs are not increased to the same degree by aprotinin as are diatomaceous earth- based (celite) ACTs. While protocols vary, a minimal celite ACT of 750 seconds or kaolin ACT of 480 seconds, independent of the effects of haemodilution and hypothermia, is recommended in the presence of aprotinin. Consult the manufacturer of the ACT test regarding the interpretation of the assay in the presence of aprotinin.~~

~~* Fixed Heparin Dosing~~

~~A standard loading dose of heparin, administered prior to cannulation of the heart, plus the quantity of heparin added to the prime volume of the cardiopulmonary bypass circuit, should total at least 350 IU/kg. Additional heparin should be administered in a fixed-dose regimen based on patient weight and duration of cardiopulmonary bypass.~~

~~* Determination of Heparin Levels~~

~~Protamine titration, a method that is not affected by aprotinin, can be used to measure heparin levels. A heparin dose response, assessed by protamine titration, should be performed prior to administration of aprotinin to determine the heparin loading dose. Additional heparin should be administered on the basis of heparin levels measured by protamine titration. Heparin levels during bypass should not be~~

~~allowed to drop below 2.7 U/ml (2.0 mg/kg) or below the level indicated by heparin dose-response testing performed prior to administration of aprotinin~~.

The partial thromboplastin time (PTT) and activated partial thromboplastin time (APTT) are similar and become immeasurable with high doses of heparin. Therefore, APTT and PTT should not be used to monitor anticoagulation with heparin in patients undergoing cardiopulmonary bypass graft surgery.

In patients undergoing cardiopulmonary bypass graft surgery with aprotinin therapy, one of the following methods is recommended to maintain adequate anticoagulation:

1. **Individualized heparin and protamine management should be considered to reduce postoperative coagulation abnormalities and bleeding complications in cardiac surgery with cardiopulmonary bypass (CPB). Individualized heparin management or titration is based on computer-based heparin dosing systems, anti-Xa measurements or blood heparin measurements in addition to the Activated Clotting Time (ACT). Anti-Xa measurement and blood heparin measurements are unaffected by aprotinin and should be carried out following test-manufacturer's notices.**
2. **In the absence of individual heparin dosing tools, it is recommended that ACT tests are performed at regular intervals based on institutional protocols, and heparin doses have to be given accordingly. The required target ACT is dependent on the type of activator and equipment used. Elevations of kaolin and celite ACT are expected in aprotinin-treated patients during surgery, and in the hours after surgery. In patients undergoing cardiopulmonary bypass with aprotinin therapy, a minimal celite ACT of 750 seconds or kaolin ACT of 480 seconds is recommended to maintain anticoagulation, independent of the effects of haemodilution and hypothermia. ACT tests using a mixture of activators should be carried out following test-manufacturer's notices.**

Protamine management

As the protamine test is unaffected by aprotinin ~~I~~in aprotinin treated patients the neutralisation of heparin by protamine after discontinuation of cardiopulmonary bypass should ~~either be based on a fixed ratio to the amount of heparin applied or be controlled by a protamine titration method~~**be carried out following test-manufacturer's notices.**

~~Important: aprotinin is not a heparin-sparing agent.~~

…

Renal impairment

Results from ~~recent~~**prior** observational studies indicate that renal dysfunction could be triggered by aprotinin, particularly in patients with pre-existing renal dysfunction. An analysis of all pooled placebo-controlled studies in patients undergoing coronary artery bypass graft (CABG) has found elevations of serum creatinine values >0.5 mg/dL above baseline in patients with aprotinin therapy (see section 5.1).

~~Careful consideration of the balance of risks and benefits is therefore advised before administration of aprotinin to patients with pre-existing impaired renal function or those with risk factors (such as concomitant treatment with aminoglycosides)~~.

An increase in renal failure and mortality compared to age-matched historical controls has been reported for aprotinin-treated patients undergoing cardiopulmonary bypass with deep hypothermic circulatory arrest during operation of the thoracic aorta. ~~Adequate anticoagulation with heparin must be assured (see also above)~~.

Careful consideration of the balance of risks and benefits is therefore advised before administration of aprotinin to patients with pre-existing impaired renal function or those with risk factors (such as concomitant treatment with aminoglycosides).

Mortality

Information on mortality from randomized clinical trials is provided in section 5.1.

…

A publication by Fergusson et al **in** 2008 analyzed data from a randomized controlled trial, Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART), and reported a higher mortality rate in aprotinin-treated patients compared to those treated with tranexamic acid or aminocaproic acid.

…

4.5 Interaction with other medicinal products and other forms of interaction

Aprotinin has a dose-dependent inhibitory effect on the action of thrombolytic agents, e.g. streptokinase, urokinase, alteplase (r-tPA). **Special attention to coagulation should be paid in patients receiving active thrombolytic agents known to be aprotinin targets.**

Renal dysfunction could be triggered by aprotinin, particularly in patients with pre-existing renal dysfunction. **Drugs with a potent nephrotoxic profile (such as ~~A~~a**minoglycosides **and renin-angiotensin-aldosterone system inhibitors)** are a risk factor for renal dysfunction. **Special attention to kidney protection should be paid when exposing patients to both aprotinin and other drugs that could trigger a kidney dysfunction.**

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4.8 Undesirable effects

Summary of the safety profile

The safety of aprotinin has been evaluated in more than 45 phase II and phase III studies including more than 3800 patients exposed to aprotinin. In total, about 11% of aprotinin-treated patients experienced adverse reactions. The most serious adverse reaction was myocardial infarction. **The safety of aprotinin has been monitored in the NAPaR between February 2016 and November 2020. Of the 6682 entered patients, the rate of adverse drug reaction was 1.1%.** The adverse reactions should be interpreted within the surgical setting.

Tabulated summary of adverse reactions

Adverse drug reactions based on all placebo-controlled clinical studies with aprotinin sorted by CIOMS III categories of frequency (aprotinin n=3817 and placebo n=2682; status: April 2005) **and based on the NAPaR** are listed in the table below:

Not known: cannot be estimated from the available data

MedDRA Standard System organ class	**Common** **⩾ 1/100 to < 1/10**	**Uncommon** **⩾ 1/1,000 to < 1/100**	**Rare** **⩾ 1/10,000 to < 1/1,000**	**Very Rare** **< 1/10,000**
Immune system disorders		**Allergic reaction** **Anaphylactic / anaphylactoid reaction**	~~Allergic reaction~~ ~~Anaphylactic / anaphylactoid reaction~~	Anaphylactic shock (potentially life threatening)

Blood and lymphatic system disorders				Disseminated intravascular coagulation Coagulopathy
Cardiac disorders		Myocardial ischaemia Coronary occlusion/ thrombosis Myocardial infarction Pericardial effusion		
Vascular disorders		Thrombosis, **embolic stroke**	Arterial thrombosis (and its organ specific manifestations that might occur in vital organs such as kidney, lung or brain), **Pulmonary embolism**	~~Pulmonary embolism~~
Renal and urinary disorders		Oliguria, **acute kidney injury**~~acute renal failure,~~ renal tubular necrosis		
General disorders ~~or~~**and** administration site conditions				Injection and infusion site reactions Infusion site (thrombo-) phlebitis
Investigations	**Blood creatinine increased**			

* Adverse Drug Reactions derived from post-marketing reports are printed in bold italic

…

5.1 Pharmacodynamic Properties

…

The Nordic Aprotinin Patient Registry (NAPaR), a multicenter non-interventional active surveillance post-authorisation study, aimed, among other outcomes, to measure the incidence of safety outcomes. A subgroup of 1,384 patients undergoing an isolated CABG

(iCABG) was treated with aprotinin. In-hospital mortality was 1.3% (95% CI: 0.73%, 1.96%). Incidences of myocardial infarction and thromboembolic events (TEEs) were 0.9% (95% CI: 0.39%, 1.39%) and 2.5% (95% CI: 1.63%, 3.28%), respectively. Renal dysfunction (postoperative rise in creatinine level >0.5 mg/dL) and renal failure (postoperative rise in serum creatinine level >2.0 mg/dL) were observed with incidences of 2.7% (95% CI: 1.82%, 3.55%) and 0.15% (95% CI: 0.02%, 0.54%), respectively. Within 24 hours following the procedure 1.3% (95% CI: 0.73%, 1.96%) of patients underwent re-exploration for bleeding. When comparing with a historical control from literature, the findings from the NAPaR were essentially in accordance with the known safety profile of aprotinin in the approved indication.

Amendments to be included in the relevant sections of the Package Leaflet (new text **underlined and in bold,** deleted text ~~strike through~~)

4. Possible side effects

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Other side effects are:

Common: may affect up to 1 in 10 patients

- **abnormal kidney function test (blood creatinine increased)**

Uncommon: may affect up to 1 in 100 patients

- chest pain (myocardial ischaemia, coronary occlusion / thrombosis), heart attack (myocardial infarction)
- leakage of heart fluid into the surrounding body cavity (pericardial effusion)
- blood clot (thrombosis)
- **reduced or interrupted blood supply to the brain (stroke)**
- kidney disease (acute ~~renal failure~~**kidney injury**, renal tubular necrosis)
- passing less urine than is normal
- **severe allergic reaction (anaphylactic / anaphylactoid reaction)**

Rare: may affect up to 1 in 1,000 patients

- blood clot in blood vessels (arteries)
- **blood clot in the lungs (pulmonary embolism)**
- ~~severe allergic reaction (anaphylactic / anaphylactoid reaction)~~

Very rare: may affect up to 1 in 10,000 patients

- swelling on or around the location of the injected skin (injection and infusion site reactions, infusion site (thrombo- phlebitis)
- ~~blood clot in the lungs (pulmonary embolism)~~
- severe blood clotting disorder that results in tissue damage and bleeding (disseminated intravascular coagulation)

- inability of the blood to clot or coagulate normally (coagulopathy)
- severe allergic shock (anaphylactic shock), which is potentially life threatening

Annex III

Conditions to the Marketing Authorisation(s)

Changes to be made to the conditions of the marketing authorisation(s) of medicinal product(s) containing the active substance intravenous aprotinin concerned by the non-interventional imposed PASS final report

The marketing authorisation holder(s) shall change the following condition(s) (new text **underlined and in bold**

The conditions for the marketing authorisation holder(s) of a DHPC, a registry and a restricted distribution shall be replaced by the below condition(s), to be completed within the stated timeframe:

The Marketing Authorisation Holder (MAH) should submit within 6 months the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, to the National Competent Authorities for approval.

The educational programme is aimed at reducing off-label use of intravenous aprotinin and educating healthcare professionals about its key risks and how to ensure adequate anticoagulation during its use.

The MAH should ensure that in each Member State where intravenous aprotinin is marketed, all healthcare professionals who are expected to prescribe, dispense or use intravenous aprotinin have access to/are provided with the following educational package:

Physician educational material:

- **The Summary of Product Characteristics**
- **Guide for healthcare professionals (with cover letter where applicable), containing the following key elements:**
    - **The benefit/risk balance of aprotinin has not been established for any indication outside the authorised indication. Uncertainty remains on the role of aprotinin in risks of mortality and severe haemorrhage in off-label use, therefore aprotinin should not be used when CABG surgery is combined with another cardiovascular surgery.**
    - **The key risks associated with the use of aprotinin and the importance of adequate anticoagulation monitoring of patients who receive aprotinin.**

In addition, the MAHs which have an RMP in place should submit to their National Competent Authority an updated RMP within six months in order to address the following issues:

- **above updates**
- **effectiveness assessment of the physician educational material**
- **comprehensive update of the RMP**

Annex IV

Timetable for the implementation of this position

Timetable for the implementation of the position

Adoption of CMDh position:	July 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	20 December 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	20 January 2024