1 Abstract

Title	Non-interventional post-authorisation safety study (PASS) of pattern of use of Nordic Aprotinin Short title: Nordic Aprotinin Patient Registry (NAPaR) Date: 31-MAY-2021 (PASS Follow-up Report, Version 1.0) Database Extraction Point: 02-NOV-2020 Main author: Anne-Lise Rossi, Medical Advisor, Nordic Pharma
Keywords	Aprotinin, bypass, cardiac surgery, heart surgery, registry
Rationale and background	The NAPaR registry was a condition for the marketing authorisation of Nordic Aprotinin and was an additional risk minimisation measure described in the European Risk Management Plan (EU RMP). It recorded information on utilisation of aprotinin (once available on the market) in patients at cardiac surgery centres. Results presented here are based on the follow-up analysis performed 56 months after completion of data entry of first patient.
Research question and objectives	Primary objectives: Monitor pattern of use of aprotinin and record utilisation information Measure adverse events (AEs) incidence identified as safety concerns in the EU RMP Measure effectiveness of risk minimisation measures as described in the EU RMP and close monitoring of adherence to Summary of Product Characteristics (SmPC) recommendations
Study design	Multicentre, non-interventional PASS with active surveillance via patient exposure registry.
Setting	Decision to treat with aprotinin made by treating physician(s) according to clinical judgment.
Subjects and study size, including dropouts	Inclusion criteria: all patients exposed to aprotinin at all participating cardiac surgical centres fulfilling criteria of restricted distribution in participating European countries. No exclusion criteria. Nordic initially estimated 12,000 to 50,000 patients would be included in the registry over 3 years (i.e. 2.5%–10% patients undergoing isolated Coronary Artery Bypass Graft (CABG) in concerned countries) (protocol version 1.1.3). In the protocol version 2.1 dated 26-MAR-2020, the sample size was updated based on the occurrence of events of specific interest (such as type of procedure, death, thromboembolism, stroke) with a reasonable precision. To meet primary objectives with 95% confidence interval and a maximum margin error of 1.56%, 3,951 patients were to be included.
Variables and data sources	Data source: electronic registry accessed through web portal, designed to collect uniform data on patients exposed to aprotinin. Data collected during routine clinical practice were entered into the electronic Case Report Form.
Results	Results presented herein focus on adult patients and were obtained from 9 participating countries: United Kingdom, France, Germany, Belgium, Sweden, Finland, Ireland, Austria and Norway.

	Up to Month 56 Data Extraction Point, 5,448 adult patients were treated with aprotinin, including 1,384 patients (25.4%) with an isolated CABG (iCABG) and 4,064 patients (74.6%) with other cardiac procedures. 347 patients (6.6%; N=5,296, available data) died before discharge. All deaths except 18 occurred in patients treated with other procedures, resulting in a higher mortality rate in this group (8.3% *versus* 1.4% with iCABG). Three hundred and seventeen (317) patients (6.0%, N=5,278) experienced at least one thromboembolic event. All thromboembolic events except 33 occurred in patients treated with other procedures, resulting in a higher incidence in this group (7.2% *versus* 2.5%). Six hundred and forty (640) patients (12.2%, N=5,234) presented renal dysfunction and 441 (8.6%, N=5,159) required post-operative renal dialysis. Incidence of renal dysfunction and dialysis was higher in patients treated with other procedures (15.5% and 10.9%, respectively) than in patients treated with iCABG (2.7% and 1.7%, respectively). Seventy four (74) cases of adverse drug reactions were reported (anaphylactic reactions in 12 patients, renal dysfunctions and urinary disorders in 47 patients, thromboembolic events in 13 patients and renal dysfunctions and urinary disorders associated with thromboembolic events in 2 patients). Two (2) patients were exposed to aprotinin during pregnancy or breastfeeding. Of the 5,404 patients who were monitored for coagulation, 2,809 (52.0%) had anticoagulation monitoring as recommended in the SmPC. Of patients with available data 94.5% received an aprotinin test dose, and 78.0% received a total aprotinin dose < 7.0 million KIU (maximal dose recommended by the SmPC).
Discussion	The majority of patients receiving aprotinin, underwent other cardiac procedures than iCABG. Aprotinin use in adults seemed to be associated with a good safety profile. Incidence of death, thromboembolic events, and renal dysfunction/dialysis was in the range of expected incidences. This was more pronounced in patients undergoing iCABG and for whom safety events occurred with a lower rate than in the literature, in particular in patients treated with iCABG. Seventy four (74) ADRs were reported since the start of the registry. During the interval period, the SmPC and risk minimisation measures were generally followed by the investigators.
Marketing authorisation holders	NORDIC GROUP B.V.
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