Trasylol (aprotinin)

Guide for Healthcare Professionals

This Guide was required by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) as part of an educational programme aimed at reducing off-label use of intravenous aprotinin, educating healthcare professionals about its key risks and how to ensure adequate anticoagulation during its use.

Therapeutic indication of aprotinin

Aprotinin is indicated for prophylactic use to reduce blood loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery).

Aprotinin should only be used after careful consideration of the benefits and risks, and the consideration that alternative treatments are available.

The safety and efficacy in children below 18 years of age have not been established, therefore aprotinin should not be used in those aged under 18 years.

Uncertainty on the role of aprotinin in risks of mortality and severe haemorrhage in off-label use

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 associated with the use of aprotinin in real-life. The NAPaR results are in accordance with the known safety profile of aprotinin, supporting a positive benefit-risk balance in the approved indication. However, there was significant off-label use of aprotinin outside of the approved indication.

The study showed an increased mortality, and an increased risk of severe haemorrhage in off-label use. In the absence of a comparative arm, the NAPaR was not designed to measure attributable risk associated with aprotinin and the observed higher mortality and severe haemorrhage in the off-label indications could be attributed to the high-risk profile of both the patients and the more complex cardiovascular surgeries. Therefore, uncertainty remains on the role of aprotinin in risks of mortality and severe haemorrhage in off-label use.

Table 1 below presents mortality rates and primary causes of death among all patients and according to indication.

Table 1: Mortality rates and primary causes of death (before hospital discharge) in adult patients exposed to aprotinin in the NAPaR

	Indication		**All patients**
	Isolated CABG	**Other procedures**	
All countries			
Mortality rates (before hospital discharge)			
N	1338	3958	5296
Missing	46	106	152
Yes – n (%[1])	18 (1.35%)	329 (8.31%)	347 (6.55%)
95%CI[1]	0.73%;1.96%	7.45%;9.17%	5.89%;7.22%
*p-Value**	< 0.001		
Primary causes of death (before hospital discharge)[2]			
N	18	326	344
Missing	0	3	3
Cardiac (excluding valvular) events – n (%[1])	13 (72.22%)	132 (40.49%)	145 (42.15%)
Others – n (%[1])	3 (16.67%)	86 (26.38%)	89 (25.87%)
Neurological events – n (%[1])	0 (0.00%)	38 (11.66%)	38 (11.05%)
Haemorrhagic events– n (%[1])	0 (0.00%)	21 (6.44%)	21 (6.10%)
Embolic/thrombotic events (other than cardiac) – n (%[1])	0 (0.00%)	19 (5.83%)	19 (5.52%)
Infection – n (%[1])	1 (5.56%)	15 (4.60%)	16 (4.65%)
Pulmonary – n (%[1])	1 (5.56%)	8 (2.45%)	9 (2.62%)

[1]Missing values were excluded from the calculation of percentages.

[2]Reported by >2% in the overall population.

*Chi Square

CABG: Coronary Artery Bypass Graft; NAPaR: Nordic Aprotinin Patient Registry.

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.

Key risks associated with the use of aprotinin

- Allergic and anaphylactic reactions
- Renal impairment
- Thrombosis

Detailed information concerning risks associated with the use of aprotinin, including special warnings and precautions for use, are described in the Summary of Product Characteristics (see sections 4.4 and 4.8).

Importance of adequate anticoagulation monitoring of patients who receive aprotinin

Thromboembolic events including myocardial ischaemia, myocardial infarction, and organ-specific arterial thrombosis manifestations (that might occur in vital organs such as kidney, lung, or brain) have been reported with the use of aprotinin. Adequate monitoring of anticoagulation during cardiopulmonary bypass is essential for the effective use of aprotinin during isolated coronary artery bypass graft surgery.

Detailed information on laboratory monitoring of anticoagulation is available in the Summary of Product Characteristics (see section 4.4).

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance at www.hpra.ie.

Should you require any further information relating to the use, supply, or prescribing of aprotinin, please contact Nordic Group B.V. [Guen Flannigan, Nordic Pharma Limited, info@nordicpharma.ie 01 4688999]