VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Patients have congenital or acquired antithrombin (AT) deficiency develop significant thromboembolic complications, generally involving the deep veins. The lifetime risk of developing venous thromboembolism (VTE) depends on the type of antithrombin deficiency. In patients with congenital AT deficiency, the risk of thrombosis is estimated to be 1% per year, starting at age 15 years. The overall lifetime risk of developing a thrombotic event in patients with congenital AT deficiency is estimated to range from 50% to 85%.

In patients with acquired deficiency, the risk of developing VTE is higher in those patients who have reactive site defects as compared to heparin-binding site defects. Estimated lifetime risk of thrombosis in acquired mutations has been reported to range from 6 to 20%, depending on the mutation site.(Patnaik 2008, Maclean 2007)

VI.2.2 Summary of Treatment Benefits

Antithrombin III NF is a very important physiological inhibitor of blood coagulation. Antithrombin deficiency may be congenital or it may be acquired within the framework of a large variety of clinical disorders. Left untreated, patients with antithrombin deficiency are at an increased risk for onset and progression of thrombotic and thromboembolic disorders. The benefit of Antithrombim III NF is its ability to be used prophylactically as well as be used as a treatment for thrombotic and thromboembolic

events. Antithrombin III NF may be particularly beneficial in patients with congenital antithrombin deficiency who are undergoing surgical procedures, and during pregnancy and delivery. In addition, Antithrombin III NF may be of particular value in patients who experienced an inadequate or lack of response to heparin. For patients experiencing thrombosis in the presence of nephrotic syndrome or inflammatory bowel disease, Antithrombin III NF may be of particular value. Finally, patients with severe liver failure who are hemorrhaging or plan to undergo surgical intervention may benefit from Antithrombin III NF, particularly if they are treated with coagulation factor concentrates.

VI.2.3 Unknowns Relating to Treatment Benefits

There is no evidence in the literature to suggest that the treatment benefits of Antithrombin III are any different as a result of age, gender, and/or race/ethnicity.

VI.2.4 Summary of Safety Concerns

Table 20. Important Identified Risks

Risk	What is Known	Preventability
Allergic reactions (Hypersensitivity and anaphylactic reactions)	Hypersensitivity reactions can range from non-serious skin reactions to life-threatening or fatal anaphylactic reactions.	The Antithrombin III Summary of Product Characteristics (SmPC) and Package Leaflet (PL) include information regarding the risk of hypersensitivity reactions. Patients who have a known hypersensitivity to Antithrombin III must not receive Antithrombin III.

Table 21. Important Potential Risks

Risk	What is Known
Brain bleeds in preterm infants with lungs complications. (Intracranial bleeds in infants with respiratory distress syndrome (IRDS))	The prevention of brain bleeds in preterm infants is not an indication for the Antithrombin III therapy
Spread of infectious disease (Transmission of infectious agents)	Careful selection of blood and plasma donors is made to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses; however, the risk cannot totally be excluded.
Potential for interaction with heparin	There is a potential for bleeding when these substances are administered concomitantly.

Table 22. Missing Information

Risk	What is Known
Lack of data in pediatric patients	There are not enough data on the use of Antithrombin III in children to confirm safety.
Lack of data in pregnant and lactating females)	There are not enough data on the use of Antithrombin III in pregnant and lactating females to confirm safety.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks, and recommendations for minimizing 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 minimization measures.

The Summary of Product Characteristics and the Package Leaflet for Antithrombin III can be found in the Antithrombin III EPAR page.

This medicine has no additional risk minimization measures.

VI.2.6. Planned Post-Authorization Development Plan

There are currently no plans to initiate any Baxalta-sponsored studies to further study the safety or efficacy of Antithrombin III in the post-authorization setting.

Studies which are a Condition of the Marketing Authorization

None of the above studies are conditions of the marketing authorization.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Major Changes to the Risk Management Plan Over Time

Table 23. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
2.0	19 April 2017	Hypersensitivity and anaphylactic reactions upgraded to important identified risk	Previous term Hypersensitivity reactions (including anaphylaxis) was renamed to Hypersensitivity and anaphylactic reaction PRAC recommendation the AT III PSUSA procedure (PSUSA 3159-201512)
		Intracranial bleeds in infants with respiratory distress syndrome (IRDS) added as an important potential risk	PRAC recommendation the AT III PSUSA procedure (PSUSA 3159-201512)