PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for *atenativ* (Antithrombin III)

This is a summary of the risk management plan (RMP) for *atenativ*. The RMP details important risks of *atenativ*, how these risks can be minimised and how more information will be obtained about *atenativ's* risks and uncertainties (missing information).

atenativ's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *atenativ* should be used.

I. The medicine and what it is used for

atenativ is authorised for congenital antithrombin deficiency and acquired antithrombin deficiency (see SmPC for the full indication). It contains human plasma-derived antithrombin as the active substance and it is given by intravenous injection.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of *atenativ*, together with measures to minimise such risks and the proposed studies for learning more about *atenativ's* risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of *atenativ* is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of *atenativ* are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of *atenativ*. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

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List of important risks and missing information	
Important identified risks	– Hypersensitivity reactions, including anaphylactic reactions – Heparin interaction; thrombocytopenia
Important potential risks	– Increased risk of intracranial bleeding with IRDS – Suspected transmission of pathogen infection
Missing information	– Use in pregnant or breastfeeding women – Use in paediatric patients

II.B Summary of important risks

Important identified risk: Allergic (hypersensitivity) reactions, including severe, sudden allergic (anaphylactic) reactions	
Evidence for linking the risk to the medicine	As with any protein product given into blood vessels, allergic-type hypersensitivity reactions may occur. Usually, patients recover fully after treatment but in some cases, allergic reactions may be serious.
Risk factors and risk groups	Patients with a history of previous reactions to plasma-derived products or known hypersensitivity to any of the constituents of the drug.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3, 4.4 and 4.8 PL Sections 2 and 4 SmPC Section 4.4 where advice is given on monitoring of patients for any symptoms throughout the infusion period. PL Section 4 where advice is given on immediately stopping the administration in case of suspected allergy or hypersensitivity. SmPC Section 4.4 and 4.8 as well as PL section 4 where a description of early signs and symptoms of hypersensitivity is included. SmPC Section 4.4 where advice is given for treating shock.

Important identified risk: Heparin-induced low levels of platelets (thrombocytopenia)	
Evidence for linking the risk to the medicine	The effect of *atenativ* is greatly enhanced by the administration of heparin at the same time. Heparin-induced thrombocytopenia may be serious or even fatal, depending on the site and type of thrombosis.
Risk factors and risk groups	• Patients receiving heparin and *atenativ* concomitantly. • Patients with type II heparin-induced thrombocytopenia (HIT) • HIT patients who develop thrombotic complications

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Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.5 PL Section 2 SmPC Sections 4.4 and 4.5 where advice is given on monitoring patients with an increased risk of bleeding who concurrently receive heparin and antithrombin clinically and biologically.

Important potential risk: Suspected transmission of pathogen infection	
Evidence for linking the risk to the medicine	When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on from donors to patients. These include careful selection of blood and plasma donors 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. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administrated, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.
Risk factors and risk groups	Patients with a depressed immune system are regarded to be at particular risk of developing infectious diseases induced by any virus. Parvovirus B19 infection may be serious for pregnant women (infection of the baby) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or abnormal breakdown of red blood cells).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 PL Section 2 SmPC Section 4.4 and PL Section 2 where advice is given on appropriate vaccination for patients in regular/repeated receipt of human plasma-derived antithrombin products. SmPC Section 4.4 and PL Section 2 where advice is given on recording of the name and batch number of the product every time *atenativ* is administered to a patient. Additional risk minimisation measures: None

Important potential risk: Increased risk of bleeding within the skull (intracranial bleeding) in patients with Infant Respiratory Distress Syndrome (IRDS)	
Evidence for linking the risk to the medicine	Data from published clinical trials and systematic reviews concerning the use of antithrombin III products, like *atenativ*, for the treatment of premature infants in the unapproved indication of Infant Respiratory Distress Syndrome (IRDS) suggest an increased risk of intracranial bleeding and mortality in the absence of a demonstrated beneficial effect.
Risk factors and risk groups	Neonates with IRDS
Risk minimisation measures	Routine risk communication: SmPC Sections 4.4

Missing information: Use in pregnant or breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 PL Section 2

Missing information: Use in paediatric patients	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of *atenativ*.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for *atenativ*.