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**BY E-MAIL**  
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Mag. Helga Lacina  
Bundesamt für Sicherheit im Gesundheitswesen  
Regulatorische Angelegenheiten  
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**SUBJECT: CLINICAL RATIONALE FOR ANTITHROMBIN CONCENTRATE IN ACQUIRED ANTITHROMBIN DEFICIENCIES**

Dear Mag. Lacina

PPTA has been made aware that the Bundesamt für Sicherheit im Gesundheitswesen has requested PPTA member companies to provide information on conducted or planned studies on the indication “acquired antithrombin deficiency” for antithrombin III products marketed in Austria.

Both indications, hereditary and acquired deficiency, are licensed in Austria.

We believe that the request for clinical studies in acquired antithrombin deficiency is unwarranted because the use of antithrombin III in acquired deficiency is in line with current medical practice in Europe.

Antithrombin deficiency may be congenital or it may be acquired within the context of a variety of clinical disorders. An acquired deficiency of antithrombin may be due either to increased consumption or loss of protein, or to defective synthesis of antithrombin.

The administration of antithrombin concentrate is indicated in patients with a plasma antithrombin activity below 70% of normal, for prophylaxis and treatment of thrombotic and thromboembolic disorders. Infusions of antithrombin concentrate have shown clinical utility in the literature in the following situations:

- surgical procedures, or pregnancy and delivery in patients with congenital antithrombin deficiency;
- inadequate or absent response to heparin;
- existence or risk of disseminated intravascular coagulation (e.g. with multiple trauma, septic complications, shock, pre-eclampsia and other disorders associated with acute consumption coagulopathy);
- treatment or prophylaxis of thrombosis in patients with nephrotic syndrome or inflammatory bowel disease;
- adjunctive treatment of thrombosis prophylaxis during surgical interventions, or haemorrhage in patients with severe liver failure, particularly if patients are treated with coagulation factor concentrates (e.g. PCC).

Several small trials have suggested efficacy of antithrombin concentrate in various clinical situations of acquired deficiency. Although none of the trials have demonstrated statistically significant efficacy regarding so-called 'hard' clinical endpoints, the evidence appears strong enough to support clinical utility in a number of diseases:

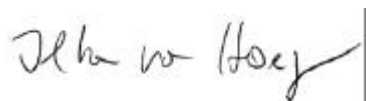
- Improved maternal and fetal outcome in pre-eclampsia;
- Prevention of DIC related symptoms in leukaemia under L-aporaginase therapy;
- Faster resolution, and prevention of multi-organ dysfunction in veno-occlusive disease;
- Improved heparin effectiveness, and quenching of coagulation activation during extra corporal circulation;
- Decreased duration of DIC, and related morbidity in conditions typically associated with activated coagulation, such as sepsis. Clinical benefit was visible especially if no concomitant heparin was used.

The situations where antithrombin concentrate is utilized are usually complex, and the diseases are often caused by multiple factors. It is clearly understood that antithrombin concentrate does not serve as a curative treatment, but it has demonstrated clinical benefits as an important adjunct. The published reports clearly demonstrate that the add-on therapy with antithrombin conferred clinical improvements, and allowed faster resolution of the underlying disease.

In view of the available clinical evidence and the current clinical practice in Europe the clinical use of antithrombin in a variety of acquired deficiencies, therefore, appears to be appropriate. In addition, antithrombin supplementation does have a favourable safety profile, particularly without co-administration of heparin.

We hope that you will consider our arguments and remain at your disposal for further discussions at any time of your convenience.

Yours sincerely,



Dr. Ilka von Hoegen  
Senior Director, Quality and Safety