*Recommendation*

# Emergency management in patients with haemophilia A and inhibitors on prophylaxis with emicizumab: AICE practical guidance in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET

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## ABSTRACT

Emicizumab has been approved in several countries for regular prophylaxis in patients with congenital haemophilia A and FVIII inhibitors because it substantially reduces their bleeding risk and improves quality of life. However, although significantly less frequent, some breakthrough bleeds may still occur while on emicizumab, requiring treatment with bypassing or other haemostatic agents. Thrombotic complications have been reported with the associated use of activated prothrombin complex concentrates. In addition, when surgery/invasive procedures are needed while on emicizumab, their management requires multidisciplinary competences and direct supervision by experts in the use of this agent. Given this, and in order to expand the current knowledge on the use of emicizumab and concomitant haemostatic agents, and reduce the risk of complications in this setting, the Italian Association of Haemophilia Centres (AICE) here provides guidance on the management of breakthrough bleeds and surgery in emergency situations in patients with haemophilia A and inhibitors on emicizumab prophylaxis. This paper has been shared with other National Scientific Societies involved in the field.

**Keywords:** *haemophilia A, emicizumab, emergency, FVIII inhibitors, bypassing agents.*

## INTRODUCTION

Emicizumab currently provides an important treatment option for long-term prophylaxis of bleeding in patients with congenital haemophilia A and inhibitors against factor VIII (FVIII)[1]. However, this novel therapeutic strategy challenges the organisation of Hemophilia Treatment Centres (HTC) which must implement specific protocols to manage and follow-up these patients in order to assure optimal efficacy and safety, appropriate laboratory testing, and the careful assessment of potentially negative drug interactions. While haemophilia treaters (HT) are gaining more and more experience in these aspects of their work through their participation in clinical studies and hands-on real-world practice, the management of breakthrough bleeding or urgent invasive procedures still requires

careful attention and appropriate guidance, particularly for non-specialised caregivers. The UK Haemophilia Centre Doctors' Organisation has addressed this task by publishing an *interim* guidance paper for the treatment of bleeding episodes and surgery in patients on emicizumab prophylaxis[2]. Similar recommendations have recently been reported by a French specialist network[3].

Scientific evidence on the clinical management of inhibitor patients on emicizumab has been growing during the last 1-2 years[1,4,5] and, on this basis, the Italian Association of Haemophilia Centres (AICE) has decided to draft a guidance paper on the management of breakthrough bleeding, surgery and emergency situations in these patients. The management proposals were prepared by the AICE *ad hoc* Working Group taking into account the data in the literature and the clinical experience gained at the network's centres; these were shared and agreed with the AICE members. A final document, approved through an online consultation in May 2019 and published on the AICE website[6], underwent a further multidisciplinary discussion with other National Scientific Societies involved in the clinical and laboratory management of patients in the emergency setting. One representative from each of these societies contributed to the revision of the present manuscript.

## EMICIZUMAB: GENERAL INFORMATION

Emicizumab (Hemlibra®, F. Hoffmann - La Roche, Basel, Switzerland) is a bi-specific, humanised monoclonal antibody which bridges factor (F)

IX/activated (FIX) and FX/activated (FX) and leads to activation of FX, thus mimicking the physiological function of activated FVIII[7]. The drug has been recently approved in several countries for the prophylaxis of bleeding episodes in patients with congenital haemophilia A and inhibitors to FVIII of all ages; in Italy, the cost of emicizumab is reimbursed by the national healthcare system in patients with FVIII level <2% and HR inhibitors (historical maximum peak >5 BU/mL). The drug is not licensed for use in acquired haemophilia A.

Emicizumab is injected subcutaneously once weekly, at 3 mg/kg during the first 4 weeks (loading dose) and subsequently at 1.5 mg/kg (maintenance dose)[1]. By using this schedule, the steady-state of plasma concentration of emicizumab is usually achieved after the first 4 doses, remaining stable thereafter with an average plasma level of 40-50 µg/mL[7].

Emicizumab reduces bleeding frequency, especially of spontaneous bleeds, but it does not fully normalise the coagulation process. Therefore, patients may still present bleeding after trauma or, although rarely, spontaneously, and thus treatment with bypassing agents may be required. In addition, bypassing agents may be needed to manage surgery or invasive procedures, and the timing of their administration and the doses to be used are decided according to clinical circumstances.

## GUIDANCE FOR THE USE OF BYPASSING AGENTS DURING PROPHYLAXIS WITH EMICIZUMAB

- Bypassing agents should be discontinued at least 24 hours before starting prophylaxis with emicizumab. This cautionary approach is the result of the observed occurrence of venous thromboembolism (VTE) or thrombotic microangiopathy (TMA) in patients on emicizumab treated with activated prothrombin complex concentrate (aPCC, FEIBA®, Baxalta Innovations, Vienna, Austria; now Takeda) for breakthrough bleeding[1]. These adverse events occurred when the dose of aPCC was >100 U/kg/day for longer than 24 hours, while no such events were observed when aPCC was used at lower doses and/or for shorter periods or during treatment with recombinant activated FVII (rFVIIa, NovoSeven®, Novo Nordisk, Bagsværd, Denmark)[1,5].
- The titre of anti-FVIII antibodies should be checked prior to starting emicizumab to assess the possible usefulness of FVIII concentrate at least until anamnestic response occurs.
- If treatment with bypassing agents is needed, rFVIIa is the first-choice option, while aPCC should be used (≤50 U/kg) when clinical response to rFVIIa is poor or other therapeutic options are not available.
- Patients on prophylaxis with emicizumab should be trained as to the dose of rFVIIa to be used as home-treatment when required. Patients and their caregivers should be aware that the HTC must be informed immediately once bleeding has occurred, even if this is only suspected (see below). The initial dose should be 90-120 µg/kg[5], to be repeated 2-4 hours apart according to the severity of bleeding and the clinical response, as recommended by the HTC. The suggested dose and schedule are based on the safety analysis conducted on the data from the HAVEN clinical programme on the concomitant use of rFVIIa for the treatment of breakthrough bleeds in patients receiving



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emicizumab prophylaxis[5]. A megadose of rFVIIa (270 µg/kg) should be avoided, even as a single infusion. As usually recommended for patients with inhibitors, to guarantee timely and accurate treatment, patients on prophylaxis with emicizumab must have available at home at least 2-3 treatment doses of rFVIIa at 90-120 µg/kg each to be used when required and to take with them when they travel or are on vacation, and when accessing Emergency Units (EU) at hospitals.

- As with other patients with inhibitors, patients on prophylaxis with emicizumab should be provided with an identification card issued by the HTC. This should report the diagnosis, the most recent available inhibitor titre, ongoing treatment, and recommendations on first-line therapy with bypassing agent (dose and regimen) to be used for evident or suspected bleeding or to manage surgery/invasive procedures. In addition, useful contact details of the HTC should also be provided, especially those to be used in emergency situations.

## GUIDANCE FOR LABORATORY TESTING OF INHIBITOR PATIENTS ON EMICIZUMAB PROPHYLAXIS

In patients on prophylaxis with emicizumab, activated partial thromboplastin time (aPTT) and all clotting aPTT-based tests are not reliable[8,9]. The aPTT is normalised after the first injection of emicizumab, although clotting activity does not normalise. Furthermore, plasma FVIII activity assay performed with the one-stage clotting assay and FVIII-deficient plasma (aPTT-dependent) will provide a very high level of FVIII, which is not reliable. Thus, aPTT and FVIII coagulant activity are generally not useful for clinical and laboratory monitoring because their apparently normal results could be misinterpreted by the clinician. However, aPTT may reveal poor adherence or lack of response to treatment due to the development of anti-drug antibodies (ADA)[10], as the test will be prolonged for very low plasma concentration of emicizumab (<5 µg/mL)[7]. The prothrombin time-derived assay underestimate fibrinogen levels and the Clauss method should be used to obtain reliable results[8,9]. **Tables I** and **II** summarise the influence of emicizumab on the tests most commonly used in patients with haemophilia A and inhibitors and on other coagulation assays.

**Table I** - *Influence of emicizumab on the tests commonly used in patients with haemophilia A and inhibitors*

| Assay | Results in the presence of emicizumab | Guidance |
|---|---|---|
| **Activated partial thromboplastin time (aPTT)** | Over-responsive (shortening) | Cannot be used/ interpreted |
| **FVIII-one-stage assay** | Over-responsive (normal, supranormal values) | Cannot be used/ interpreted |
| **Modified one-stage assay calibrated against emicizumab** | Responsive to emicizumab (dose-dependent) | May be used to measure emicizumab concentrations |
| **FVIII chromogenic assay, human reagents** | Responsive to emicizumab (dose-dependent) | May be used to estimate emicizumab activity |
| **FVIII chromogenic assay, bovine reagents** | Responsive to FVIII and insensitive to emicizumab | May be used to measure FVIII activity |
| **Bethesda assay based on one-stage assay** | False-negative | Cannot be used to measure inhibitors to FVIII |
| **Bethesda assay based on chromogenic assay, bovine reagents** | Responsive to FVIII and inhibitors | Can be used to measure FVIII inhibitors |

FVIII: factor VIII.

**Table II** - *Influence of emicizumab on other coagulation tests*

| Assay | Results in the presence of emicizumab | Guidance |
|---|---|---|
| **PT** | Unaffected (or slightly prolonged) | Can be used/ interpreted |
| **Fibrinogen (Clauss method)** | Unaffected | Can be used/ interpreted |
| **D-dimer** | Unaffected | Can be used/ interpreted |
| **Thrombin time** | Unaffected | Can be used/ interpreted |
| **Antithrombin activity** | Unaffected | Can be used/ interpreted |
| **Protein C anticoagulant (APTT-based) activity** | Reduced | Chromogenic assay should be used |
| **Protein S anticoagulant (APTT-based) activity** | Reduced | Antigen measurement should be used |
| **Activated protein C resistance (APTT-based)** | Reduced APC-ratio | Cannot be used/ interpreted |
| **Search for lupus anticoagulant** | Over-responsive | Cannot be used/ interpreted |
| **Activated coagulation time (ACT)** | Shortening | Cannot be used/ interpreted |

PT: prothrombin time; APTT: activated partial thromboplastin time.

- The laboratory should always be promptly informed that the patient is on prophylaxis with emicizumab. It is highly recommended that phone contacts of the patient's HTC should be provided to these laboratories in case of an emergency.
- Determining plasma concentration of emicizumab is not usually necessary for clinical purposes or to help decide how to manage acute bleeding episodes.
- If replacement treatment with a FVIII concentrate is started in patients with low-titre inhibitor, plasma FVIII levels must be assayed using the chromogenic method with bovine reagents.
- During prophylaxis with emicizumab, titration of inhibitors to FVIII must only be carried out by the FVIII chromogenic method with bovine reagents. FVIII inhibitor should be measured before starting treatment with emicizumab and then at least every 6 months by using the above-mentioned assay. This information is necessary to decide whether FVIII replacement therapy can be used in the presence of low-titre inhibitor should there be a poor clinical response to bypassing agents.

## MANAGEMENT OF INHIBITOR PATIENTS ON EMICIZUMAB IN THE EMERGENCY UNIT

- When a patient on prophylaxis with emicizumab accesses the hospital EU, it is crucial a prompt identification through an ID card issued by the HTC. This should confirm the type and severity of haemophilia, the most recent inhibitor titre, the ongoing therapy, the dose of rFVIIa to be administered as the first treatment in case of suspected or active bleeding, and emergency contact details of the HTC.
- The HTC in charge of the patient must be contacted as soon as possible to decide on how to manage the emergency, the treatment with bypassing agents, the use of additional or alternative haemostatic therapy such as antifibrinolytics, local haemostasis, and the possible use of FVIII concentrate. If an institutional HTC is not available on call, the protocol for the emergency management of inhibitor patients should be formally agreed between the EU and the HTC, and approved by the hospital management, so that a reference document can subsequently be provided if required.
- If a bleeding episode is suspected or the patient reports recent trauma, the diagnostic work-up to confirm or exclude ongoing bleeding is mandatory. Inhibitor patients on prophylaxis with emicizumab are protected against the occurrence of most spontaneous bleeding episodes, but this protection is not absolute. There is always a residual risk of haemorrhage after trauma, or in the case of surgery or invasive procedures.
- If highly suspected or active bleeding is present, or in case of major trauma, or if the patient requires an urgent invasive procedure, rFVIIa 90-120 μg/kg should be infused in the EU before even contacting the HTC, as indicated on the patient's ID card issued by the HTC.
- The use of aPCC during emicizumab prophylaxis must only be considered for patients who do not respond to the first-line treatment with rFVIIa. However, the administration of aPCC must be specifically prescribed by the HT in charge of the patient.
- It is also recommended that EU physicians do not modify the therapeutic schedule with emicizumab (i.e., administration of an adjunctive dose or skipping the subsequent dose) unless prescribed by the HTC responsible for the patient.
- If the patient accesses the EU because of symptoms other than haemorrhage, consideration must be given to the fact that thromboembolic complications, although rare, may occur, especially in patients on emicizumab prophylaxis who have self-infused bypassing agents. Therefore, a diagnostic work-up for the differential diagnosis or the exclusion of such complications is advisable.

## MANAGEMENT OF BLEEDING OR SUSPICION OF BLEEDING IN INHIBITOR PATIENTS ON EMICIZUMAB PROPHYLAXIS

Because of the relatively long half-life of emicizumab (around 4-5 weeks)[7], all the recommendations reported in this and the next paragraphs should be applied with caution also to patients who discontinued emicizumab <6 months earlier. Therefore, in these cases, the management, therapeutic strategies and laboratory testing should be discussed and agreed with the HTC in charge of the patient.

As with all other patients with inhibitors, those on emicizumab prophylaxis must be trained by the HTC as to the first therapeutic intervention to adopt in case of bleeding or trauma. They should be told to immediately contact the HTC and to evaluate the opportunity to self-infuse a dose of 90-120 μg/kg of rFVIIa, which could be repeated every

2-4 hours, depending on the site or severity of the bleeding. In the case of unclear joint symptoms, patients should consider waiting until they have contacted the HTC to avoid unnecessary treatment and risks.

- In the case of life-threatening/debilitating haemorrhage (i.e., intra-cranial) or bleeding events considered severe because of the anatomical site or related symptoms (i.e., muscle haematoma with risk of compartmental syndrome), the patient should be strictly monitored and re-evaluated by the HT after the first 2-3 doses of rFVIIa to decide how to proceed with the subsequent doses and how to monitor the laboratory parameters.
- In the case of moderate haemorrhage, it is possible to prolong the interval between doses of rFVIIa (every 6 hours) if bleeding is controlled and clinical improvement is observed.
- In the case of bleeding which does not respond, or only partially responds, to the first 3 doses of rFVIIa, the patient must be re-evaluated by the HT. If the patient is not hospitalised, the reassessment at the HTC within 24-48 hours is needed, to monitor the clinical outcome and to up-date the therapeutic prescriptions.
- In the case of moderate trauma or minor haemorrhage, topical measures (e.g., applying ice, local haemostasis, antifibrinolytics for topical use) can be sufficient to prevent/stop bleeding. Tranexamic acid for systemic (10 mg/kg i.v. or 15-25 mg/kg per *os* every 8 hours) or topical use can be sufficient to obtain complete control of bleeding episodes such as epistaxis, gum bleeding (mouthwash with a 10 mL 5% solution for 2 minutes, four times a day), or other mucosal bleeds. Moreover, tranexamic acid can be associated to rFVIIa treatment for the management of moderate-severe bleeding episodes.
- If loss of efficacy of emicizumab is suspected because of poor patient compliance (missed administration of the drug for many weeks) or for the development of ADA[10] (although this is rare), it is advisable to perform an aPTT, which will be prolonged for very low plasma concentration of emicizumab (<5 μg/mL)[7]. In this case, the HTC must contact the laboratories they work with that are able to provide support with further diagnostic procedures.
- In the case of a severe haemorrhage or poor response to rFVIIa, the inhibitor titre must be measured by a Bethesda assay with a bovine reagent-based FVIII chromogenic assay. It should be remembered that the Bethesda clotting assay with human reagents will give false negative inhibitor results in patients on emicizumab, and this should be taken into account. The inhibitor evaluation is mandatory to evaluate possible treatment with FVIII concentrate when the inhibitor titre is <5 BU/mL.
- In the case of severe haemorrhage that is not sufficiently responsive to rFVIIa, and in the presence of a high-titre inhibitor (>5 BU/mL), aPCC at an initial dose ≤50 U/kg is the second-line treatment. If this dose of aPCC is not sufficient to control bleeding, repeated low doses of aPCC every 8-12 hours could be considered. The infusions must be administered under medical supervision in hospital maintaining the whole 24-hour dosage <100 U/kg to reduce the risk of VTE and/or TMA.
- If the administration of aPCC is required for ≥24 hours, daily monitoring is recommended. This should include: tests for disseminated intravascular coagulation ([DIC] D-dimer, fibrinogen, platelet count), tests for haemolysis (lactate dehydrogenase [LDH], bilirubin, haptoglobin, reticulocytes), renal function, cell blood count, and peripheral blood smear for schistocytes.
- The use of recombinant porcine FVIII, susoctocog alfa (rpFVIII, Obizur®, Baxalta Innovations, Vienna, Austria; now Takeda) may represent a rescue option when there is no response to bypassing agents or in case FVIII concentrate cannot be used because of high-titre anti-human FVIII inhibitors, if anti-porcine FVIII inhibitor activity is absent or low-titre. Susoctocog alfa could also be considered when contraindications to second-line treatment with aPCC (patients with previous VTE on aPCC therapy, or with VTE or TMA when aPCC was used as second-line therapy while on emicizumab prophylaxis) are present.
- Susoctocog alfa is not licensed for treatment of congenital haemophilia with inhibitors and the off-label use of this product is under the direct responsibility of the HT; treatment must be authorised by hospital management. Moreover, no evidence from the literature about treatment regimens to be used in case of prophylaxis with emicizumab is available.
- Before the use of rpFVIII, anti-porcine FVIII inhibitor should be assayed. However, this should be performed before starting treatment with emicizumab because its

measurement is based on aPTT and would, therefore, be affected by emicizumab.
- Plasma levels of FVIII on rpFVIII treatment are measured by an APTT-based assay; therefore, in the case of emicizumab prophylaxis, this test is unreliable.
- It is recommended that all second-line treatment approaches must be prescribed and administered under the direct responsibility and monitoring of the HT.

## MANAGEMENT OF SURGERY IN INHIBITOR PATIENTS ON EMICIZUMAB PROPHYLAXIS

Information on the management of surgery in inhibitor patients on emicizumab is limited but rapidly growing[11-15].
- Most minor procedures (e.g., central venous catheter removal/insertions, dental extractions, endoscopies with biopsies) can be safely carried out even without prophylaxis with bypassing agents[11,12,15]. However, a dose of rFVIIa 90-120 µg/kg should be infused by EU physicians as specified on the patient ID card if a HT is not available.
- The administration of rFVIIa can be repeated at the same dose of 90-120 µg/kg every 2-4 hours during and after surgery, after evaluating the bleeding risk, the type of surgery, and the advice of the HT. Tranexamic acid at standard doses can be associated to rFVIIa, as previously indicated.
- In the case of minor procedures, particularly at mucosal sites, tranexamic acid alone at standard doses could be used; however, rFVIIa must be available in case of bleeding complications, as prescribed by the HT and agreed by the other specialists involved.
- In major invasive procedures at high risk of bleeding, spinal or epidural anaesthesia should be avoided, if possible. A pre-operative dose of rFVIIa 90-120 µg/kg is recommended, to be repeated every 2-4 hours, evaluating the clinical outcome and following the instructions of the HT.
- In cases of major surgery, and in the presence of an inhibitor titre <5 BU/mL, a high dose of FVIII concentrate is advisable, after consideration of the possible option of continuous infusion and at least daily monitoring of FVIII plasma levels by a bovine reagent-based FVIII chromogenic assay[12]. Once there is an anamnestic response, rFVIIa will be administered at the doses and frequencies previously reported.
- In the case of severe haemorrhagic complications during or after surgery, failure to respond to rFVIIa, and in the presence of a high-titre inhibitor (>5 BU/mL), the use of aPCC should be considered at a daily dose of ≤100 U/kg, starting with a dose of ≤50 U/kg. During emicizumab prophylaxis, the concomitant use of tranexamic acid alongside aPCC is not recommended.
- The use of rpFVIII as a rescue therapy could be considered, taking into account all the limitations and considerations concerning the off-label use of this product, as reported above.
- If aPCC administration is required for ≥24 hours, monitoring is recommended with daily tests for DIC, for haemolysis (LDH, bilirubin, haptoglobin, reticulocytes), renal function, cell blood count, and peripheral blood smear for schistocytes.
- In the case of major surgery, it is recommended that the evaluation and management of second-line treatments is overseen by the HT in charge of the patient.

The management of emergency situations in patients with haemophilia A and inhibitors on emicizumab prophylaxis is summarised in the algorithm reported in **Figure 1**.

## DISCUSSION

This AICE guideline paper adds to the other documents on the management of bleeding and surgery in inhibitor patients on emicizumab prophylaxis, provided by experts from specialised centres in the UK and France[3,4]. At variance with these publications, our document is primarily referred to management of emergency situations in the setting of our healthcare network and local infrastructures. The need for a multidisciplinary approach, in part explored by our French colleagues[4], is one of the main issues addressed in our document, with a special focus on practical guidance and protocols agreed and formally approved by hospital Authorities. Our management proposals have been shared with laboratory and clinical specialists working in the emergency setting, and cover issues concerning patient information and training, laboratory testing, and therapeutic strategies. The clinical experience about emicizumab is rapidly growing and this means clinical recommendations have to be continuously updated. In this respect, based on the most recently available safety analysis of data from the HAVEN programme[5], we were able to suggest safe higher



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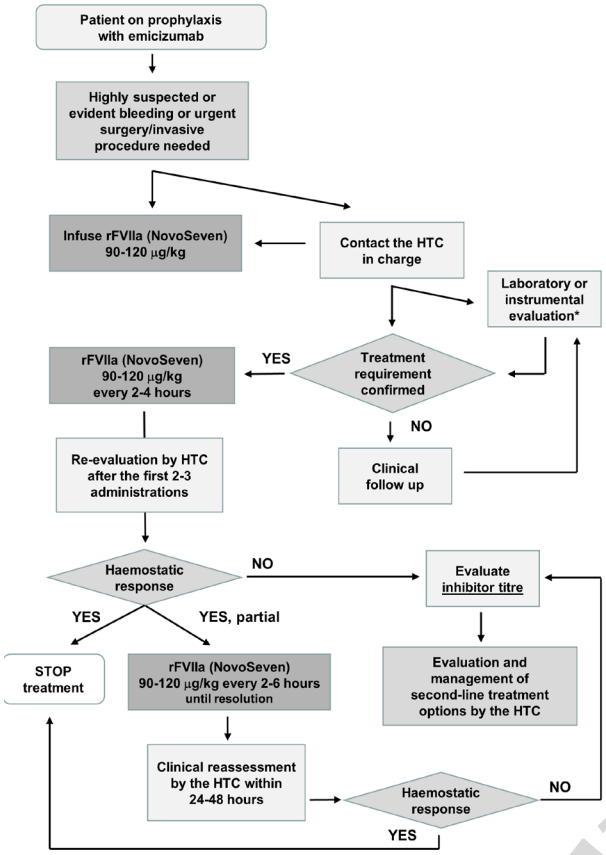


**Figure 1 -** Algorithm for management of emergency situations in patients with haemophilia A and inhibitors on emicizumab prophylaxis

It is recommended that the HTC be consulted to evaluate and confirm treatment with bypassing agents, to define clinical outcome and, thereafter, to determine duration of treatment. In case of no/unsatisfactory response to the first-line treatment, the evaluation and management of second-line therapy approaches, as described in this document, should be made under the direct control and responsibility of the HTC. In cases in which an institutional HTC on-call is not available, the referral protocols will be granted and agreed between the HTC and the Emergency Unit, and formally approved by the hospital management. *If necessary to clarify the diagnosis and to decide indication to treatment. HTC: Hemophilia Treatment Centres; rFVIIa: recombinant activated FVII.

rFVIIa doses for the treatment of breakthrough bleeds as compared with the advice given in the UK guidance paper[3] and that reported in the French document[4]. New safety information also allows treatment with rFVIIa as soon as possible to be recommended, even at home when a bleed is highly suspected, not only when it actually occurs, as recommended by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO)[3]. Management with different haemostatic agents (bypassing agents, human and porcine FVIII concentrates) is, on the whole, comparable in our and the previously published guidance papers; however, criteria and limitations for rescue treatment with susoctocog alfa are more clearly stated in the present document, including laboratory issues which must not be overlooked. Finally, in line with recent data on ADA[10], the suspicion of this complication by prolonged APTT, in cases of loss of efficacy of emicizumab, has been specifically introduced in our recommendations, underlining the need for confirmation by specialised laboratories.

## CONCLUSIONS

In its framework of a multidisciplinary approach, our document highlights the key role of the HT who ideally should be promptly available to manage or supervise any emergency situation. However, in Italy, many HTCs are not formally recognised and operate within 21 different regional health systems where frequently 24 hour-clinic services and specialised coagulation laboratories are not available. Therefore, this document should be shared with all professionals involved in the management of emergency situations (Emergency Units, Laboratories, Hospital Authorities), together with the responsible HTC, to define and adopt institutional operative protocols. AICE, indeed, considers it to be of the utmost relevance that the issue of management of emergency situations, particularly in patients with inhibitors and in those on prophylaxis with emicizumab, should be tackled with appropriate decision-making procedures. These should be part of the comprehensive management of patients with inherited bleeding disorders, for whom appropriate and accurate management and networking have a strong impact on the efficacy and safety of treatments, as well as on the correct use of economic resources.

## DISCLOSURE OF CONFLICTS OF INTEREST

*GC acted as a consultant for Roche and as a member of the speaker bureau and/or advisory board sponsored by Ablynx, Alexion, Bayer, Baxalta/Shire, CSL Behring, Kedrion, Novo Nordisk, Pfizer, Roche, Sobi, Uniqure and Werfen. CS acted as paid consultant/advisor/speaker for Bayer, CSL Behring, Shire/Takeda, Novo Nordisk, Amgen, Novartis, Pfizer, Roche and Sobi. AC acted as a paid consultant or member of the speaker bureau for Bayer and Novo Nordisk. MEM acted as paid consultant/advisor/speaker for Bayer, CSL Behring, Novo Nordisk, Pfizer, Sobi, Bioverativ, Octapharma, Roche, Grifols, Kedrion, Shire and Biotest. RCS acted as a member of*

*the speaker bureau or advisory board sponsored by Bayer, CSL Behring, Roche and Shire/Takeda. AR acted as paid consultant/advisor/speaker for Bayer, CSL Behring, Shire/Takeda, Novo Nordisk, Kedrion, Pfizer, Roche and Sobi. ES acted as a member of the speaker bureau and/or advisory board sponsored by Shire/Takeda, Bayer, Pfizer, CSL Behring, Novo Nordisk, Grifols, Bioverativ, Sobi, Octapharma, Kedrion, Spark, Uniqure and Roche.*

*The other Authors declare no conflicts of interest.*

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## APPENDIX

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