

# New opportunities in Haemophilia treatment: Efmoroctocog Alfa for patients with Haemophilia A

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## ABSTRACT

Recently new opportunities are emerging for improving the way patients with Haemophilia A are treated. Among these opportunities, efmoroctocog alfa is a first-in-class recombinant factor VIII-Fc fusion protein (rFVIIIIFc) produced by recombinant DNA technology with an extended half-life compared with conventional FVIII preparations. The available evidence coming from an Italian HTA report indicates that efmoroctocog alfa provides an effective alternative to conventional FVIII preparations (including standard rFVIIIs) for the management of Haemophilia A. Moreover, by reducing the frequency of injections required, it has the potential to reduce treatment burden, and hence improve adherence to prophylaxis and patient Quality-of-Life.

Key words: Haemophilia A, efmoroctocog alfa, HTA

Haemophilia A (HA) is an X-linked recessive bleeding disorder caused by mutations in F8 gene (Xq28), resulting in factor VIII (FVIII) deficiency and characterized by spontaneous hemorrhage or prolonged bleeding. HA accounts for 80–85% of patients with Haemophilia and affects approximately 1 in 5,000 male births [1]. According to the Italian National Registry of Congenital Coagulopathies, in 2017 the Italian patients with HA were 4,179: 44.3% with severe form (N = 1,850), 13.7% with moderate form (N = 572) and 42.0 % with mild form (N = 1,757) [2].

The disorder is clinically heterogeneous with variable severity. Table 1 shows clinical features and age at diagnosis in relation to disease severity. In general, first bleeding episodes occur when affected infants start learning to crawl. Bleeding events, that can happen spontaneously, most often occur into the joints (hemarthroses) and in the muscles (hematomas), but any site may be involved following trauma or injury [3]. Recurrent joint bleeding may lead to chronic arthropathy and progressive damages to the joint tissues that result in chronic pain, disabilities and poor quality of life (QoL) [4].

The mainstay of HA treatment is replacement therapy by intravenous (IV) administration of coagulation FVIII [1]. The products currently in use in Europe are plasma-derived factors VIII (pdFVIII) and concentrates produced by recombinant DNA technology (rFVIII) [5]. Replacement therapy can be administered on demand for a clinically evident bleeding episode, or as a prophylaxis [4]. Prophylaxis consists of IV administration of FVIII concentrate with the main objective of preventing bleeding episodes, hemophilic arthropathy and preserving normal musculoskeletal function. Currently, early long-term prophylaxis is the standard of care to prevent joint bleeding and chronic arthropathy in patients with severe hemophilia [4, 6, 7]. However, benefits of prophylaxis have been shown even in patients starting this regimen later in life by reducing bleeding frequency and joint deterioration and improving QoL [8, 9].

Prophylaxis treatment presents several advantages in terms of clinical outcomes; however, some clinical aspects still need to be improved in order to address optimal patients' compliance. The development of inhibitors is the most serious complication of replacement therapy, occurring in approximately 30% of patients with severe HA which makes replacement therapy ineffective. Moreover, frequency of treatment due to short half-life of conventional FVIII concentrates, difficult venous access and costs may represent significant critical issues [5]. Indeed, existing standard rFVIII products have an average half-life of approximately 12 hours. This short half-life requires prophylaxis treatment to be given every other day to maintain a trough level of FVIII greater than 1% to prevent spontaneous bleeding. The requirement for relatively frequent IV administration of FVIII may negatively impact on treatment adherence. The development of extended half-

life (EHL) factor concentrates aims to reduce the treatment burden [1].

Recently, new opportunities such as efmoroctocog alfa (Elocta) that is a first-in-class recombinant FVIII-Fc fusion protein (rFVIIIFc) [10], are emerging for improving the HA treatment. It has an EHL compared with conventional FVIII preparations, including standard half-life rFVIII products [11]. Furthermore, it has a prolonged half-life of about 1.5 times the comparator (Advate) (geometric mean: 19.0 vs 12.4 h, respectively; p < .001) used in a phase 3 pivotal study (A-LONG study) that evaluated safety, efficacy, and pharmacokinetics of efmoroctocog alfa [12]. For this reason, efmoroctocog alfa represents the first treatment with prolonged protection against bleeding episodes with prophylactic IV injections administered every 3-5 days in a significant proportion of patients [11].

A large amount of data in adults and children collected from pivotal phase 3 studies [12-14], have demonstrated the long-term efficacy of efmoroctocog alfa for the treatment of acute bleeding episodes, perioperative management and routine prophylaxis in previously treated patients (PTPs) with severe HA. These clinical studies demonstrated that among PTPs on individualized efmoroctocog alfa prophylaxis, all but one of those aged ≥12 years and three-quarters of those aged <12 years reduced their injection frequency compared with their pre-study regimen. Moreover, the extension of these studies showed that most subjects on efmoroctocog alfa prophylaxis regimen were able to maintain or extend their infusion interval. FVIII replacement therapy with efmoroctocog alfa was generally well tolerated in PTPs, and no subjects developed an inhibitor during the studies [15].

An analysis of data concerning the experience in the Italian context has been recently published and real-world findings confirm clinical study results [16]. Evidence from 13 Italian patients with mean 18 months-follow up after switch from prophylaxis with standard half-life rFVIII to rFVIIIFc shows the reduction both in the number of infusions (average 40%), and in the consumption of FVIII (average 12.5%), leading to favorable clinical outcomes and improvement of treatment satisfaction linked to the reduced burden of infusions [16].

In order to provide additional evidence about the sustainability related to the efmoroctocog alfa introduction in the Italian context, a report of Health Technology Assessment (HTA) has been recently published [17]. In Italy, this report represents one of the few HTA in the Rare Diseases (RDs) field. Recently, even in Italy, Scientific Community and Public Health policy makers acknowledged the opportunity to increase HTA methodology and evidence generation in the RDs field [18].

The report evaluated clinical, organizational, economic and ethical implications of the efmoroctocog alfa introduction into the Italian National Health System (NHS) [17].

As unique EHL rFVIII reimbursed by NHS in Italy up to

now, efmoroctocog alfa allows the clinical physicians to personalize treatment according to specific patient's needs, based on the flexible dosing regimen. This translates into a smaller burden of treatment for patients and caregiver and improved treatment adherence and QoL [10].

The data from the efficacy/safety studies indicate the possibility of reducing the injections frequency of efmoroctocog alfa as well as a favorable profile in terms of bleeding rate reduction, in particular at joints' level. Furthermore, no study patients developed inhibitors during treatment [14, 17], although no data are yet available for previously untreated patients (PUPs).

From organizational domain, the HTA of efmoroctocog alfa underlines the importance of a multidisciplinary management of haemophilic patients (including a hematologist, a nursing coordinator, an expert in musculoskeletal diseases - usually physiatrist, orthopedist and/or physiotherapist -, a laboratory medicine expert, a psychologist or a social worker) [4, 17]. This integrated management takes into account all aspects of the patient's life and represents the key to a correct preservation of joint health.

Moreover, a cost-effectiveness analysis (CEA) and a budget impact analysis (BIA) have been developed to assess the long-term benefit and the short-term sustainability of efmoroctocog alfa for the treatment of patients with severe HA, from the perspective of the Italian NHS. CEA demonstrated that prophylaxis regimens with efmoroctocog alfa represent an important option for HA management being more effective and less expensive compared to the standard rFVIII considered in the model. On the other hand, there is also an incremental cost-effectiveness ratio both in terms of Euro/Quality Adjusted Life Years (QALY) and Euro/LY when efmoroctocog alfa used in prophylaxis regimen is compared with other comparators used on demand. These results are mainly due to the prolonged half-life of efmoroctocog alfa and to its efficacy in reducing Annualized Bleeding Rates (ABRs). Beyond certain limitations, sensitivity analyses have demonstrated the solidity of the results [17]. These results are consistent

with another cost-effectiveness analysis [19] where rFVIIIfc proved to reduce costs and improved QoL incorporating real-world dosing and joint health data in the Italian setting.

BIA, built on a three-year horizon, showed that the gradual introduction of efmoroctocog alfa in the clinical practice as prophylaxis regimen, in substitution of standard rFVIII, is associated with a growing saving for the NHS. The cumulated saving over a three-year period amount to about € 9.7 million, corresponding to about € 4,685/patient/year saving. In addition, when considering the population of patients treated on-demand, the gradual utilization of efmoroctocog alfa leads to a saving of € 710,783 for the NHS in the three-year period [17]. Further data on long-term efficacy/safety profile, and the inclusion of indirect costs in the economic evaluation would be useful to allow additional economic assessments, especially regarding the long-term preservation of joint health and related social/economic costs that might be avoided. Moreover, it will be critical to further increase consistency of available evidence by enriching the perspectives of different stakeholders such as patients, caregivers and patient associations.

Finally, according to the available literature, the use of efmoroctocog alfa in the treatment of hemophilic patients is ethically justified, according Italian NHS ethical framework, with a positive efficacy/safety/tolerability profile and an improved risk-benefit profile related to inhibitor appearance compared to other rFVIII [17].

In conclusion, the available evidence coming from the Italian HTA report indicates that efmoroctocog alfa provides an effective alternative to conventional FVIII preparations (including standard rFVIIIs) for the HA management. Moreover, by reducing the frequency of injections required, it has the potential to reduce treatment burden, and hence improve adherence to prophylaxis and patient QoL. In light of current and future challenges that healthcare systems are facing, evidence-based approaches such as HTA are a valuable tool to support investment and disinvestment decision in health technologies [20].

**TABLE 1. Clinical features and age at diagnosis in relation to the severity of the disease [4]**

Disease severity	Clinical features	Age at diagnosis
<b>Severe form</b> (biological activity of factor VIII <1%)	-Frequent spontaneous haemorrhage, especially into joints; -Abnormal bleeding as a result of minor injuries or following surgery or tooth extraction.	≤ 2 years
<b>Moderate form</b> (biological activity of factor VIII between 1% and 5%)	-Rare spontaneous haemorrhage; -Abnormal joint bleeding as a result of minor injuries, bleeding following surgery or tooth extraction	<5-6 years
<b>Mild form</b> (biological activity of factor VIII between 6% and 40%)	-Absence of spontaneous bleeding; -Abnormal bleeding as a result of minor injuries or following surgery or tooth extraction.	At a later age (even in adulthood)

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