

## ASSESSMENT OF THE CLINICAL AND ECONOMIC IMPACT OF ADVATE IN PROPHYLACTIC TREATMENT OF HEMOPHILIA A PATIENTS

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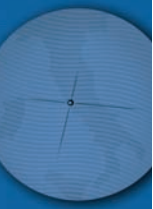
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*The Health Technology Assessment report presented in this supplement of the Italian Journal of Public Health consists of two parts, because as a service for our international readership we decided to publish the English translation of the report that appeared already in Italian (Advate per il trattamento e la profilassi dell'Emofilia A: una valutazione di HTA, 2011 Vol. 8 Nr.2, Suppl. 1) along with the new update just released by the same group of authors to provide new details and evidence about some of the most relevant elements of the assessment.*

*For the sake of readability, the main body of work appears first, while the newly released update follows.*



IJPH - 2012, VOLUME 9, NUMBER 4, SUPPL. 2

# ITALIAN JOURNAL OF PUBLIC HEALTH

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# Introduction to the Report on the Health Technology Assessment of Advate®

Flavia Kheiraoui, Walter Ricciardi

## INTRODUCTION

Around 40 years ago, *Technology Assessment* (TA) arose in response to the uncontrolled diffusion of technology. The purpose of this multidisciplinary assessment process (1) was then as now that of providing an instrument of support for arriving at decisions about the allocation of economic resources (2).

Applied originally in non-healthcare contexts, from the 1980s onwards this instrument gradually came to be utilized and adopted to support decision-making in healthcare. Due to the progressive aging of the population and an accompanying growth in awareness of the availability and potential of new healthcare technologies, the trend is for perceived healthcare needs to grow. Given that resources available to the healthcare system are by definition limited, the consequence is that resources are not able to satisfy the population's overall demand for services.

A Health Technology Assessment (HTA) evaluates the medical, economic, organizational and social aspects of the introduction and implementation, or the divestment, of healthcare technologies or interventions. It therefore takes into consideration all of the aspects that may be influenced by the technology being studied as well as all of the elements that could influence its deployment and the results it attains (3).

With its multidisciplinary nature, an HTA does not just provide an instrument of research: it is a systematic, rigorous and reproducible assessment process, accessible and validated, capable of 'bridging' between the world of science and that of political decision-making (4, 5).

It follows that, by focusing on the clinical, safety and technical effects of various healthcare technologies (6), on their performance and efficacy, on costs and cost-efficiency, on their organizational, ethical, social and cultural repercussions, an HTA is a suitable instrument for application in a

multiplicity of sectors and fields. Applications range from individual healthcare technologies (therapeutic, such as drugs, medical diagnostic devices and equipment, or preventative, such as vaccines), to medical-surgical services, and to organizational management models (refund systems, models for the dispensation of support services and welfare procedures) (7).

## Objective of the Report on the Health Technology Assessment of Advate

The objective of this project has been to develop an HTA on Advate, octocog alfa, third-generation recombinant factor VIII for the treatment and prophylaxis of bleeding episodes in patients affected by Hemophilia A in order to analyse the product's potentials and limitations in the context of the epidemiological, clinical, economic and organisational situation in Italy.

## Methodology

In methodological terms, this report has been produced through the development of consolidated activities within the working group at the Research Center for the Valuation of Healthcare Technologies at the Public Health Institute at the Università Cattolica of Rome. This working group adopted a multidisciplinary approach to the subject, applying the structure of reports that had already appeared in other contexts (8, 9). In particular, the working group tracked down, analysed and then processed available information on the subject, producing an analysis that is both comprehensive and to a large extent original.

This Assessment of the medicinal product Advate was conducted taking the following points into consideration:

- The epidemiology and burden of disease of Hemophilia A both globally and within Italy

- Clinical-therapeutic management of Hemophilia A
- The resources deployed by National Health Services and the related costs for managing Hemophilia A
- The bio-toxicity, efficacy, safety and toxicity of Advate
- Mathematical models and economic analyses of the use of Advate in the Italian context
- Scrutiny of the organizational aspects concerning the use of Advate in the Italian healthcare context
- Bioethical issues

In addition, a chapter containing the key elements for decision makers has been prepared in such a way as to provide a summary overview of findings relevant to operational decisions.

It must be stressed that the present report has been peer reviewed through a discussion of its preliminary results with a broader expert group (the External Advisory Board), which was followed by the sending of comments and suggestions. This has indeed enriched the formulation arrived at by the working group at the Research Center.

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# 1. Epidemiology of Hemophilia A globally and in Italy

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## INTRODUCTION

The word hemophilia derives from the Greek '*bema*' (blood) and '*philia*' (affection). There are various types of hemophilia: the most common form (80%) is Hemophilia A, which is due to a deficiency of clotting factor VIII. In the case of hemophilia B, or Christmas disease, there is a deficiency of Factor IX (1). The least frequent form is hemophilia C or Rosenthal syndrome, which is caused by a partial or total lack of Factor XI or PTA (Plasma Tromboplastin-Antecedent) (2).

Hemophilia A is a congenital and hereditary disease. It is due to a defect in the way blood coagulates, deriving from a lack of Factor VIII, whose gene is located on the X chromosome, thus affecting males almost exclusively. So this anomaly is transmitted in an X-linked recessive way, by so-called 'diagynic inheritance' – a term denoting the hereditary transmission of a trait from male to male or via a female (in Greek, '*dia*' meaning 'through' and '*ginaikos*', meaning woman). For this reason the disease can only express itself clinically in the male ( $X_m Y$ ). In the female carrier of the altered gene ( $X_m X$ ), the disorder is not manifest thanks to 'chromosome inactivation', i.e., due to suppression of the defective gene through the other, normal, chromosome (3). A good example of this can be seen in Queen Victoria's family tree. The Queen was a carrier of a mutation that subsequently descended through three different European royal families (Appendices 1 and 2). A typical cross that shows the X-linked nature of the disorder is that between a healthy female carrier ( $XX_m$ ) and a normal male (XY). The resulting offspring has 25% of the healthy female chromosomes (XX), 25% of the female carrier ( $XX_m$ ), 25% of healthy male (XY) and the remaining 25% of affected male chromosomes ( $X_m Y$ ).

The disease is compatible, then, with the reproduction of affected males. This is today the case with Hemophilia A, thanks to the possibility of administering Factor VIII. So we can now also observe crosses between affected males ( $X_m Y$ ) and healthy females (XX), whose offspring consist exclusively of healthy males and female carriers. It is equally possible, although actually very rare, to have a cross between an affected male ( $X_m Y$ ) and a female carrier ( $XX_m$ ), whose male offspring will be 50% affected and whose female offspring will be 50% carriers and 50% affected: this is one of the very rare cases in which it is possible to find an affected female. Whatever the case, all of the male children of a male hemophiliac will be unaffected by the disorder (Figure 1) (4).

## Physiopathology

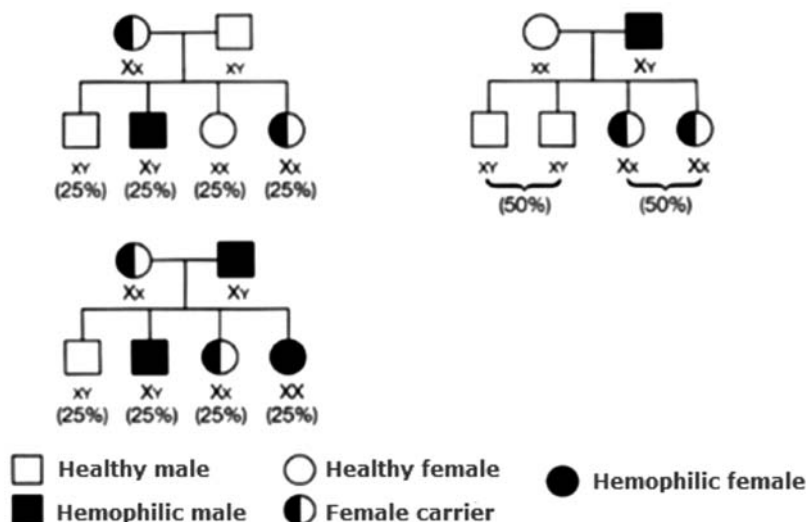
Factor VIII or *anti-hemophilia factor* is a complex plasmatic glycoprotein with a high molecular weight and single chain, which is mainly synthesized by hepatocytes. It intervenes in the blood coagulation process (6).

Coagulation is a complex process based on a network of enzymatic reactions having the purpose of stopping blood loss by forming a clot (7).

These reactions are essential for maintaining a balance between the blood's fluid and solid states: insufficient coagulation can cause hemorrhaging, while excessive coagulation can lead to thromboses, disseminated intravascular coagulation or other vascular disorders. The enzymes concerned are serine protease in type, and they activate one another via a 'cascade' mechanism. The coagulation process is triggered by tissue factor (TF), a protein that under normal conditions is expressed on the membrane of the fibroblasts. Upon endothelial damage, TF comes into contact with clotting factors and with Factor

FIGURE 1

## HEREDITARY TRANSMISSION ROUTES FOR HEMOPHILIA



A family history of hemophilia is present in 70% of cases. Nonetheless, one hemophiliac child in three is born within a family where no history of hemophilia can be traced (30% of sporadic forms, i.e. mutations starting 'de novo' or from scratch) (1, 5)

VIIa in particular, with which it forms a TF-FVIIa complex. This complex is capable of initiating the enzymatic cascade, with the involvement of Factor VIII (8).

### Diagnosis and Symptomology

Patients with suspected coagulation disease are screened using a series of hemostasis tests, including platelet count, prothrombin time test (PT) and activated partial thromboplastin time test (APTT). In cases of hemophilia, the patient will present with an extended APTT, while all of the other tests will prove normal. Hemophilia A and B are clinically indistinguishable from each other. For a correct diagnosis, which is essential for initiating the right form of treatment, it is therefore necessary to carry out further specific examinations of Factors VIII and IX (9).

In families where cases of Hemophilia are present, the females may be given a genetic test to find out whether they are carriers.

In general, hemophilia causes bleeding in the joints (knee, elbow and ankle), in the muscles and in other soft tissue (neck, tongue and gastrointestinal tract). This bleeding manifests as swelling and pain. Clinical manifestations of Hemophilia A are heterogeneous and depend on the molecular anomaly, and therefore on

the coagulating activity of factor VIII (FVIII: C). In a normal person, this activity varies between 50% and 200%. Hemophilia is classified as mild, moderate or severe according to the residual level of circulating factor VIII (10-12):

- SEVERE HEMOPHILIA: Functional FVIII <1%, the most frequent form (43%), with spontaneous bleeding, necessitating continuous substitution therapy
- MODERATE HEMOPHILIA: Functional FVIII between 1-5% (26%), with rare spontaneous bleeding episodes
- MILD HEMOPHILIA: Functional FVIII between 6-40% of normal (31%), in which there is a general absence of spontaneous bleeding

Symptomology varies with age: in cases of severe Hemophilia among neonates, episodes of prolonged bleeding may be observed following circumcision or there may be intracranial hemorrhage. Among the 1-to-6-month age group, soft tissue bleeding or bruising may be encountered and, as walking begins, episodes of intra-articular bleeding will start to appear. With increasing age, the joints represent the most common site (70-80%) of spontaneous bleeding (spontaneous hemarthrosis): the main sites are the knees (45%), the elbows (30%) and the ankles (15%).



Repeated or tardily treated hemarthroses can lead to joint deformity and ankylosis. Bleeding episodes can also occur in the muscles, in soft tissue and within the central nervous system, causing contracture, nerve paralysis, osteocystoma and muscular atrophy. Internal hemorrhaging caused by the more severe forms, can be accompanied by serious complications, depending on the area where it occurs. These include neurological damage and renal colics; some complications may be fatal (1, 13, 14). Other relatively frequent symptoms, due to infection or trauma, are epistaxis, hemoptysis and peptic ulcers, linked to the frequent use of NSAIDs (analgesics).

It should also be pointed out that there is a form of acquired Hemophilia A. This disorder arises in individuals having no personal or familial history of coagulation disorders. It is an autoimmune condition with the presence of auto-antibodies directed against coagulation Factor VIII, which interfere with its coagulating function. Acquired hemophilia is a very rare coagulation disorder, with an incidence of 1.4 cases per million/annum, although data appear to underestimate its incidence as the disorder is little known and many cases therefore fail to be diagnosed or reported (15).

### Global Epidemiology of Hemophilia A

The global prevalence of Hemophilia A is estimated on the basis of surveys conducted worldwide each year by the World Federation of Hemophilia (WFH) using data gathered from the national registries of each country (67%), from surveys carried out by hemophilia treatment centers (23%), from national surveys (3%) and from other sources (7%) (16).

According to the most recent report (2008), 108 402 subjects in 108 countries suffer from Hemophilia A. Of these, 3 987 have inhibitors against Factor VIII, 5 541 are HIV positive and 28 519 have contracted the hepatitis C virus (HCV) (16).

The literature reports an incidence of Hemophilia A of 20/100 000 births, without variations among different populaces and races (17-23), while the mean prevalence ranges between 12.8/100 000 males [Standard Deviation (SD): 6.0] in the more economically developed countries and 6.6/100 000 (SD: 4.8) in the rest of the world (24).

A recent study, based on data gathered

by the global surveys conducted each year by the WFH and from the literature, has assessed the prevalence of Hemophilia A reported in each country as it varies, when factored against national economies (24). Among the high-income nations belonging to the OECD, (*Organization for Economic Cooperation and Development*), mean prevalence varied between the figure of 5.3/100 000 for North Korean males and that of 38.6/100 000 for Iceland (24). Among high-income countries not belonging to the OECD, mean prevalence ranged between 1.0 for Saudi Arabia and 16.3 for Slovenia. Among mid-income non-OECD countries, the range was from 2.9 for Lebanon to 17.5 for Hungary and in medium-low income countries mean levels ranged from 0.1 for Indonesia to 16.2 for Macedonia. Finally, the range for low-income countries spanned 0.04 for Togo and 6.0 for Uzbekistan (24).

Figure 2 shows how approximately 70% of countries report a prevalence of 10 or lower among their male populations (24).

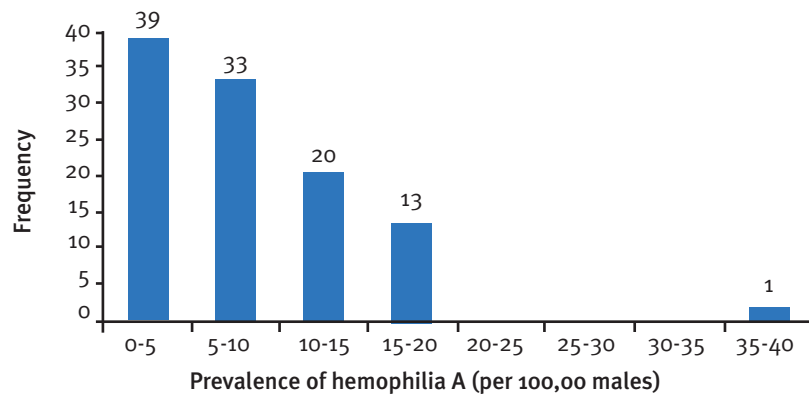
There are wide variations between different countries. Especially among low-income countries, estimates are much lower than those for richer countries, coming in lower than the expected ratio from international incidence rates (24). Possible reasons for these underestimates are: difficulties of diagnosis, difficulties in accessing treatment, scant economic resources and the shortage or even total absence of substitution therapy with factor VIII, entailing death in early life (25-29). Of all those affected, it is estimated that just 20% receive adequate substitution therapy with factor VIII (30).

According to the most recent WFH report, of those countries taking part in the survey, the United States of America (USA) had the highest absolute number of people affected by Hemophilia A, with a total of 12 386 patients, followed by India with 10 982 and Brazil, with 6 881 persons affected (16). In Europe, the most affected country in absolute terms is the United Kingdom with 4 991 sufferers, followed by Germany with 4 000 and France with 3 929 (16). Similarly, in terms of the absolute numbers of patients with clinically identified inhibitors, (antibodies that are capable of interfering with or totally blocking the activity of clotting factors), the highest number are in the USA (12 386 patients), followed by Russia (5 032 patients) and the United Kingdom (4 991 patients) (16).

In member states of the European Union,

FIGURE 2

## MEAN PREVALENCE (PER 100 000 MALES) OF HEMOPHILIA A



Histogram of the mean prevalence (per 100 000 males) of Hemophilia A for each of the 106 countries supplying data to the WFH. The figures above the columns represent the total number of countries with the mean prevalence shown as a range on the x axis (24)

Hemophilia A affects around 0.6/10 000 persons (approx. 30 000 people in total), which has led this disorder to be ranked among the so-called rare diseases (31).

Of relevance is the fact that the total number of countries reporting to use a national register has increased steadily over the years, rising from 39 in 2003 to 57 in 2006. At the same time, the number of countries not reporting the source of their data fell from 31 in 2003 to 14 in 2006 (24). Between 2003 and 2006, 44% of reporting countries stated that they used a registry, 26% derived their data from hemophilia treatment centers, and 11% used other approaches, while 19% did not indicate the source of their data to the WFH (24). This highlights how the most important issue in determining the total number of sufferers, not just globally but in each country, is the absence of standardized procedures to enable the gathering and subsequent comparison of data (24). This has an unavoidable impact on the quality of the limited available data that is used by the WFH to conduct its global surveys, and on the under-estimate of the number of cases due to incomplete recognition, to the non-representational nature of the samples and to failure to respond to surveys (24).

Although it has increased by about 50 years since the 1960s (32, 33), life expectancy among hemophilic patients remains significantly lower than that of non-sufferers, with a mortality rate twice as high as that for healthy males (34-36). Considering just patients with severe hemophilia, the death rate is 4-6 times higher

than that for non-affected males. However, when those affected by hepatitis and cirrhosis are excluded, the death rate becomes nearly identical (Table 1) (35, 36).

Apart from hemorrhaging caused by the disorder itself, the reasons behind this high death rate are HIV, AIDS and HCV infections, all of which were acquired via the plasma derivatives (including cryoprecipitates) used in treating hemophilia during the 1980s and 1990s (23, 41, 42). Indeed, starting from that very period, the percentage of deaths due to hemorrhage or circulatory complications decreased and the main cause of death became complications from AIDS (23, 41, 42). It has been estimated that during the twenty year period cited above, in the USA between 9 300 and 10 000 hemophiliacs (over 50% of the total) were infected by HIV. The figure for Japan is 1 800, for the United Kingdom 1 700 and for France it is 2 000 (43-45). A German study has reported that, since 1978, the most common cause of death for patients with Hemophilia A registered at the Center for Hemophilia in Bonn was AIDS (70.1%). This was followed by hepatitis/ hepatocellular carcinoma (HCC) (8.8%) and lastly, intracranial hemorrhage (5.8%) (46). However, following the adoption of HAART anti-retroviral therapies in 1997, the absolute number of deaths decreased from 15-20 per year to 5-10, and the main causes of death became hepatitis and HCC along with intracranial hemorrhage (46).

Apart from the HIV virus, most hemophiliacs contracted the hepatitis B

TABLE 1

LIFE EXPECTANCY AMONG PATIENTS WITH SEVERE HEMOPHILIA (37)						
REFERENCE	POPULATION	N	PERIOD	H I V STATUS	LIFE EXPECTANCY (YEARS)	
					SEVERE HEMOPHILIA	TOTAL MALE POPULATION
Darby et al. (34)	UK	2 706	1977-1998	HIV-	63	78
Chorba et al. (36)	USA	2 254*	1979-1982	HIV+/HIV-	55*	-
			1987-1990	HIV+/HIV-	41*	-
			1995-1998	HIV+/HIV-	46*	-
				HIV+	33*	-
				HIV-	72*	-
Plug et al. (38)	Netherlands	386	1972-1985	HIV+/HIV-	63	71
			1985-1992	HIV+/HIV-	61	74
			1992-2001	HIV+/HIV-	59	76
				HIV-	70	76
Triemstra et al.(39)	Netherlands	381	1986-1992	HIV+/HIV-	61	74
Rosendaal et al. (40)	Netherlands	717	1973-1986	HIV+/HIV-	66	74
Larsson et al. (29)	Sweden	948*	1961-1980	HIV+/HIV-	57	76

\*all forms of hemophilia (mild, moderate, severe); (-) data not available

(HBV) infection and/or hepatitis C (HCV): transmission of the latter, in particular, was found in a percentage of cases varying between 46% and 90%, according to different studies (47, 48). The presence of infection by these viruses represents a significant complication that cannot be disregarded: suffice it to say that among HCV-positive hemophilia sufferers, cirrhosis develops in 20% of cases (49) and that if a co-infection from HIV or from HBV is present, progression of the HCV infection is considerably accelerated (50-52).

As has already been seen with HIV, although transfusional risk from HCV was a global issue, many regional differences were found in HCV infection rates among hemophilia sufferers. This was probably due to the varying decisions taken with respect to transfusion policy by individual governments during the 1980s (Table 2) (53).

Nonetheless, while the clinical impact of HCV contamination of transfusion bags among hemophiliacs during the 1980s was greater than that deriving from HIV contamination during the same period, the response by

public health authorities to this problem was decidedly lower in its magnitude (53).

### Epidemiology of Hemophilia A in Italy

This section presents facts that emerge from an examination of the available databases and from the scientific literature concerning the epidemiology of this disease in Italy.

### Databases

The *World Federation of Hemophilia* (WFH) has recommended that all nations should set up national registries dedicated to Hemophilia and Congenital coagulation diseases (54). A detailed database was developed in Italy in 2005, dedicated to congenital and acquired coagulation diseases, and collaboration was launched between the Italian Association of Hemophilia Centers (AICE), the Department for Transfusion Methodologies (of the Hematology, Oncology and Molecular Medicine Department

TABLE 2

ESTIMATE OF THE NUMBER OF LIVING PEOPLE AFFECTED BY HEMOPHILIA AND CARRIERS OF HCV OR HIV (53)

COUNTRY (NUMBER OF HEMOPHILIACS)	NUMBER OF LIVING PERSONS AFFECTED BY HEMOPHILIA AND CARRIERS OF HCV OR HIV		YEAR OF PUBLICATION OF REPORTS REGARDING PUBLIC INQUIRIES INTO VIRAL CONTAMINATION OF TRANSFUSION BAGS	
	HCV	HIV*	HCV	HIV
USA (14 886)	4 456	1 698	-	1995
United Kingdom (6 109)	2 829	405	Scotland alone (2000)	-
Italy (5 319)	4 361	534	-	-
Japan (4 683)	2 436	871	-	-
France (4 000)	2 600	1 250	-	1991
Canada (2 772)	1 100	251	1997	1997
Australia (1 070)	534	84	2004	-
Ireland (545)	157	37	1997, 2002	2002

\*The actual total number of persons affected by Hemophilia and carriers of HIV is higher than the number of hemophiliacs still alive today, but many of these have since died from complications arising from AIDS.

of the Italian National Health Institute, ISS) with participation by the Federation of Hemophilia Associations (FEDEMO).

Following this collaboration, the National Registry of Congenital Coagulation Diseases (RNCC) was set up, gathering together data concerning coagulopathic disorders and enabling supervision of adverse reactions, of infections and the appearance of inhibitory antibodies in particular. The RNCC registers data of patients with better-known disorders such as Hemophilia A, hemophilia B (X-linked diseases) and Von Willebrand disease (an autosomal dominant disease) as well as data from patients with rarer disorders affecting other clotting factors.

The Italian National Health Institute (ISS), in collaboration with AICE, produced a paper on the RNCC (55), which reports the main results achieved by the registry.

Data for the RNCC is gathered from the Hemophilia Centers (HCs) distributed across the nation (Figure 3).

The information presented in the report was gathered indirectly through extraction using Emocard software (Appendix 3) and from the HCs, whose directors sent the therapeutic plans for coagulopathy patients directly to the Transfusional Methodology department of the ISS.

The RNCC data is rendered anonymous and

non-sensitive and the information it contains is verified using congruity and logico-formal checks (for duplication of patients, checking of birth dates, diagnoses, etc.); incongruities in the data are reported to the HCs so that they may be corrected, where possible.

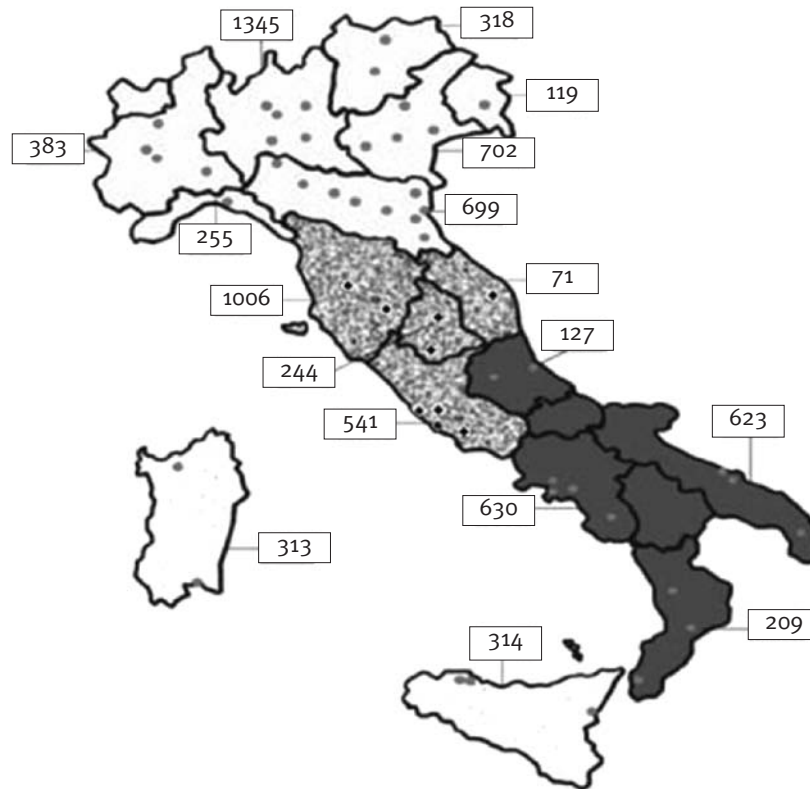
Hemophilic patients are subdivided according to severity of disorder using previously determined criteria. The therapeutic plans contain the colagulopathic diagnosis, the treatment period, the trade name of the drug prescribed, the company that produces it, dosage and the overall number of units prescribed. Patients who have developed antibodies against the infused factor during the course of their therapy have been subdivided into *high responder* patients and *low responder* patients, according to the maximum titer of inhibitor found (*high responder*:  $\geq 5$  Bethesda units; *low responder*:  $< 5$  Bethesda units).

In 2008, 49 out of the 52 HCs sent data to be processed for the register.

Data from 7 899 coagulopathy patients was evaluated: of these, approximately 42% had Hemophilia A, excluding the female *carriers* and those affected by acquired Hemophilia A. Half of the patients affected by Hemophilia A had severe Hemophilia and 36% had mild hemophilia (Table 3). On the other hand, 62 patients were suffering

FIGURE 3

DISTRIBUTION OF HEMOPHILIA CENTERS IN ITALY (MODIFIED FROM ABBONIZIO ET AL. (55)),  
WITH THE NUMBERS OF PATIENTS FOLLOWED IN EACH REGION



from acquired Hemophilia and 322 were female carriers.

With regard to distribution across age-groups, the prevalence of Hemophilia A drops off after the age of 20, although there are less obvious variations between the different age groups among the moderate and severe forms (Figure 4).

Among severe hemophiliacs, 17% developed inhibitors; among moderate hemophiliacs, this percentage was 3.5%, and it was just 0.7% among those with mild forms of hemophilia.

Furthermore, 57% of patients appearing on the RNCC were assessed for HIV markers and 43% for HCV markers. Of the HIV positive patients present on the RNCC, 77% were persons with Hemophilia A, of whom 69% had severe Hemophilia A. Of these patients with severe Hemophilia A, 19% proved to be HIV positive, while of those with moderate and mild forms, 4% and 2% respectively proved HIV positive. Of the HCV positive patients, on the other hand, 78% were

persons with Hemophilia A. Among those with the moderate form this percentage was 36% and among those with mild hemophilia, it was 22% (Table 4).

#### Review of the literature

A study conducted by Tagliaferri et al. (56), carried out in collaboration with AICE, used RNCC data relating to hemophiliac patients who died in Italy between 1980 and 2007. Questionnaires were completed investigating demographic and clinical characteristics relating to complications and any presences of comorbidity for each of the 463 died patients in the 27 centers taking part in the initiative.

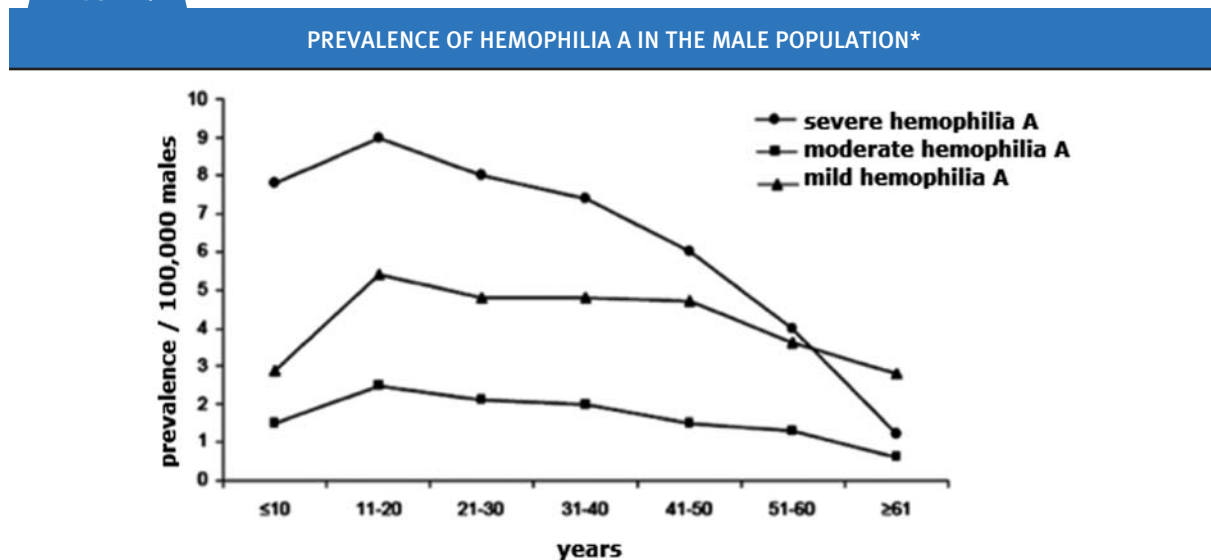
Compared to the reference population of Italian males, the Standardized Mortality Report (SMR) for hemophiliac patients fell from 1.98 (95% CIs: 1.54-2.51) in the period 1990-1999, to 1.08 (95% CIs: 0.83-1.40) in the period 2000-2007. Similarly, life expectancy for these patients rose from 64 (1990-1999) to 71 years (2000-2007).

TABLE 3

PATIENTS AFFECTED BY HEMOPHILIA A REGISTERED WITH THE RNCC			
DIAGNOSIS	MALES	FEMALES	TOTAL
Severe Hemophilia A	1 647	7	1 654
Moderate Hemophilia A	448	5	453
Mild hemophilia	1 180	16	1 196
Acquired Hemophilia A	32	30	62
Carriers of Hemophilia A	-	322	322
Total	3 307	380	3 687

Modified from Abbonizio et al. (55)

FIGURE 4



\* Subdivided for clinical severity and age group (2008) (modified from Abbonizio et al. (55))

Turning to causes of death among Italian hemophiliacs, although the Tagliaferri study reports a total of 20.2% of deaths due to hemorrhage (in the period 1980-2007), it highlights how AIDS represented the primary cause of death in these patients from 1980 onwards. However a proportional decrease in deaths attributable to HIV/AIDS was registered as they fell from 60% for the period 1990-1999 to 17.6% for 2000-2007.

On the other hand, increased life expectancy due to the checks introduced for all blood-derived products, and to the new recombinant drugs which were developed and introduced in therapy, led to these patients increasingly developing chronic degenerative pathologies

such as cardiovascular disease and tumors (57, 58). Today, hemoderivatives undergo viricide treatments and are obtained from donors at a very low risk of being carriers of infectious viruses.

For example, while during the 1990s (1990-1999) deaths due to cardiovascular disease among Italian hemophiliacs stood at 3.1% of all deaths, in 2000-2007 this percentage had tripled (9.2%). The same trend was seen for deaths due to tumors, which rise from 5% in the decade 1990-1999 to 11.4% in 2000-2007 (56).

A study recently conducted in Italy by Siboni et al. compares a group of hemophilic patients aged 65 or over with a group of non-hemophiliacs having the same characteristics of age, social status and origins. From the study it emerged

TABLE 4

## PATIENTS WITH HEMOPHILIA A FOUND TO BE POSITIVE FOR HIV AND FOR HCV

DIAGNOSIS	TOTAL PATIENTS	HIV+	HIV+/HCV+	HCV+
Severe Hemophilia A	1 654	173	141	721
Moderate Hemophilia A	453	11	7	158
Mild hemophilia	1 196	11	9	252
Total	3 303	195	157	1 131

Modified from Abbonizio et al. (55)

that hemophiliacs have more comorbidity, being affected by viral diseases (HBV, HCV, HIV), hypertension and arthropathy and have greater difficulties in their daily activities due to reduced physical capabilities and depression, although their cognitive state showed no difference to that of non-hemophiliacs. However, non-hemophiliacs proved to be more susceptible to hypercholesterolemia and cardiovascular diseases (59).

A study of hemophilic patients conducted in Tuscany using the SF-36 and EuroQOL questionnaires showed how their perceived state of well-being was lower on nearly all counts compared to the non-affected population (Table 5). Furthermore, the risk factors negatively influencing perceptions of quality of life were old age and having contracted HIV (60).

#### Epidemiology of complications associated with Hemophilia A

The most common of the complications of Hemophilia are associated with bleeding episodes: among these we find hemophilic arthropathy, which is characterized by repeated hemarthroses and a consequent chronicity of the condition, and fatal hemorrhages.

Another complication, related to the time duration of treatment, is the production of inhibitors, or alloantibodies, capable of neutralizing the action of clotting factors used in treating the disorder. Now that the risk of transmission of infective diseases has been overcome thanks to the use of new generation products, inhibitor production today constitutes one of the major complications of this disease. A description of the problem of infection is

indispensable, given the burden of disease, especially of HCV and HIV, due to the worldwide diffusion of the end of the last century.

Bleeding at the joints represents over 90% of bleeding episodes among patients affected by severe hemophilia (62, 63); it may present in acute episodes, leading to phlogosis of the affected joint, or it may, when repeated over time, lead to joint degeneration, with the onset of hemophilic arthropathy. Hemarthroses mainly affect the knee, elbow and ankle joints (64) and less frequently the hip and shoulder joints. Small joints are very rarely affected (14). As a consequence, hemophilic arthropathy that establishes itself following repeated bleeding episodes and which leads to hypertrophy of the synovia, destruction of the cartilage and osteoarthritis (65), occurs predominantly in the knee, the elbow, the hip and the shoulder (66). The incidence rates of hemophilic arthropathy, which is the most disabling of the complications of this disease, have declined over time thanks to opportunities for primary and secondary prophylaxis; however, the condition tends to set in before the age of 15-20 (67, 68). In order to give an idea of the burden of disease associated with this condition, we report the findings of a study conducted at Italian hemophilia centers which provided an estimate of the cumulative incidence of joint replacement interventions. These represent a final therapeutic resource for patients affected by hemophilic arthropathy and in the period 1987-2007 they equaled 14.3% (95% CIs 12.7%-15.9%) for patients with severe hemophilia (69).

However, 15-30% of bleeding episodes take place outside the joints, particularly in the muscles, in the retro-peritoneum and bones (68). Bleeding episodes in the muscles occur with a ratio of 1 to 4 compared to those in joints. When repetitive, these may be the cause

TABLE 5

## MEANS SCORES ATTAINED BY PATIENTS RECEIVING SF-36

SF-36 VARIABLES (N=56)	SCORES FOR HEMOPHILIACS *	GENERAL POPULATION SCORES **	DIFFERENCE BETWEEN SCORES
Physical activity (PA)	73.6±25.4	84.5±23.2	-13%
Role and physical health (RP)	64.7±42.6	78.2±35.9	-17%
Physical pain (PP) 6	6.3±29.6	73.7±27.6	-10%
General health (GH)	55.2±25.2	65.2±22.2	-15%
Vitality (VT)	62.6±19.6	61.8±20.7	1%
Social activities (SA)	74.7±24.8	77.4±23.3	-3%
Role and emotional state (RE)	65.5±42.6 7	6.2±37.2	-14%
Mental Health (MH)	68.0±21.8	66.6±20.9	2%

\*Trippoli et al. (60);

\*\*Comparative data, compared with a sample of the non-hemophilic Italian population, Apolone et al. (61).

of atrophy, compartment syndrome, fibrosis and contractions; the most affected muscles are the psoas and the quadriceps femoris (67, 68). One of the complications of intramuscular bleeding is the formation of pseudotumors or encapsulated hematomas that occur in 1-2% of the hemophilia population (70); these constitute a rare complication, but it is an important one as it may lead to the formation of fistulae, infections, internal bleeding, and bone erosion and, in some cases, the death of the patient (71).

Intracerebral hemorrhage represents one of the potentially lethal complications of the disease and is responsible for one third of deaths attributed to hemophilia (72); the risk for an individual of developing this type of hemorrhage over the course of their life is 2-8% (72). Around 1-4% of hemophiliac neonates are affected by intracerebral hemorrhage (73), independently of the method of birth used. However, most cases occur with vaginal births and particularly with assisted births (74-76). A recent review confirms that the percentage of neonates affected by this complication is around 3.5-4%, with frequencies that are between 40 and 80 times higher than among the healthy population (77). The death rate from intracerebral hemorrhage is, fortunately, decreasing over time and stands at approx. 20% (78, 79).

A series of extremely rare complications

exist, which are in some cases fatal. The literature reports multiple cases of hematoma of the epiglottis (80), cardiac tamponade (81), rupture of the spleen at birth (82) and hemorrhages of the retropharyngeal tissue (83).

We point out that severe complications may be a first manifestation of the acquired form of the disease, although it usually presents with subcutaneous hematomas, (84, 85). However, the disease may also first present, in 9% of cases, with fatal hemorrhages (83).

With regard to the development of inhibitors, the prevalence of patients affected by this problem stands at 5-7% (86), although in cases of severe and moderate Hemophilia A this may reach levels of between 7% and 18% (87).

The incidence rate for developing inhibitors in the United Kingdom has been estimated at 3.5 per 1 000 patients for cases of severe Hemophilia and at 0.84 per 1 000 for the mild and moderate forms of the disease (88, 89).

As reported in the paragraph concerning the Italian data, in this country inhibitors are found in 17% of patients with severe Hemophilia A (55).

Patients with inhibitors present higher levels of complications and disability; the European Study on Orthopaedic Status (ESOS) demonstrates a significant difference in terms of levels of arthropathy among young patients (14-35 year olds) with inhibitors compared to those



without, with an increased need for orthopedic procedures and a greater hospitalization rate for bleeding and musculo-skeletal problems (90). The same study also demonstrates that among 14-35 year olds with inhibitors, 75% had mobility problems compared to 33% in the same age group but without inhibitors; again, 50% and 28% respectively reported problems with their daily life activities and 72% against 49% reported pain or malaise with clear repercussions on their quality of life (90).

Moreover as concerning infection, we point out that before 1985, over 90% of hemophilic patients treated with plasma derivatives were affected by HCV (91-94), and that around half of these were concomitantly affected by co-infection with HIV (95).

Italian data about Hemophilia A patients, who resulted positive for the HIV and HCV tests, are discussed in the section relating to the situation in Italy as summarized in Table 4.

The course of HCV (96) and HIV (97) infections in hemophilic patients follows the same pattern as in the general population, with their attendant burden of disease.

## CONCLUSION

Hemophilia A is a congenital and hereditary disease. It is due to a defect in the way blood

coagulates, deriving from a lack of Factor VIII, whose gene is located on the X chromosome, thus affecting almost exclusively males.

Data gathered by the World Federation of Hemophilia in 108 countries report approximately 110 000 cases, predominantly of Hemophilia A, worldwide.

According to data from the National Register of Congenital Coagulation Diseases, in Italy there are approximately 4 000 people affected by this disorder. Half of these are affected by severe Hemophilia A and 36% by mild Hemophilia A.

With reference to the epidemiological evolution of the disease, the nature of the deficit indicates that incidences of Hemophilia A will remain constant, while improvements in the level of public healthcare and rising life expectancies of affected patients will lead to an increase in the numbers of those requiring anti-hemophilia treatment, with an increasing prevalence of the disease.

Apart from the problem of inhibitors, the more daunting infection-based complications that led to such heavy loss of life during the 1980s, such as AIDS and viral hepatitis, are disappearing. This is largely thanks to improved donor selection and to the virus inactivation technology to which human blood products are subjected, but above all to the ever more widespread use of recombinant factors.

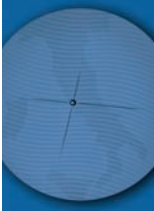
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**APPENDIX 1**

**Historical background**

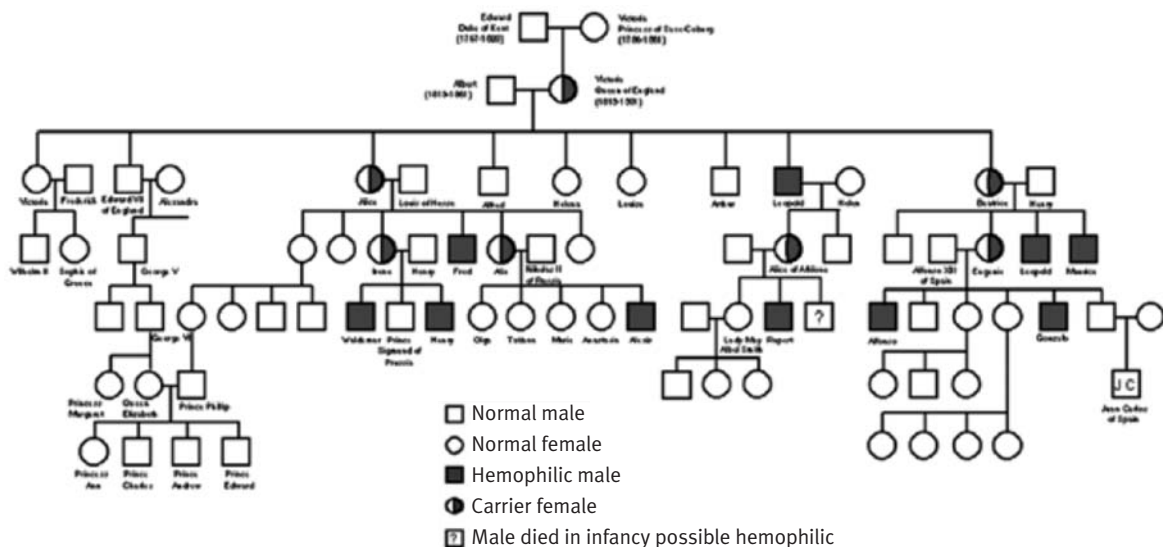
Hemophilia is also known as ‘the royal disease’ as one famous carrier was Queen Victoria (Queen of England and Ireland 1837-1901, Empress of India 1876-1901), who transmitted the condition to at least three of her children: one affected male and two certain female carriers. Eight of Victoria’s nine children married members of European royal families, and as can be seen from the family tree of Queen Victoria’s descendants, this disease can be said to have played a part in the political history of Europe from the beginning of the 20<sup>th</sup> century (1). The queen’s most ‘famed’ hemophiliac descendent was her great grandson, the little Czarvi Alessio Romanov, son of the last Czar of Russia, Nicholas II. One of the first ‘therapies’ undertaken to cure young Alessio was carried out by one of the most controversial figures in Russian history: the monk Rasputin. Rasputin won over the Czarina’s trust, and with it great political power and prestige within the royal family, through a successful intervention on the health of the Czar’s heir. Thanks to a stroke of intuition, Rasputin stopped the therapy that was being administered to treat the boy’s severe joint pains. This had been based on acetylsalicylic acid, and which therefore had the devastating side effect of causing heavy bleeding (2).

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**APPENDIX 2**

**Queen Victoria’s family tree**



## APPENDIX 3

### Emocard software

Since 2003 the Italian Association of Hemophilia Centers (AICE) has been using the *Italian Haemophilia and Allied Disorders Registry*. This registry gathers all the data supplied by the 52 hemophilia treatment centers spread across the country (1). The registry's objectives are to determine the prevalence and incidence of Hemophilia and its complications and to guide institutions towards the most appropriate management of this set of pathologies. In order to do so, Emocard software was developed as a tool to be used at all the hemophilia treatment centers in Italy. The desire for the registry and its dedicated software came from the directors of the hemophilia centers themselves, with a design remit that it should be managed entirely by the medical personnel and regularly updated. Emocard software was realized as a support for every activity carried out in a hemophilia treatment center. A record can be made of each patient's personal details, family medical history and pathology, a list of vaccinations, of examinations, HIV and HCV test results, a complete coagulation profile, data on treatment type and method, hospitalizations, surgical interventions and all the relevant laboratory data. Each patient's data is sent to a national database, which is updated every six months. The homogeneity of the data gathered is guaranteed in that the fields to be entered for each patient are codified as yes/no, numerical or multiple-choice response data.

Each patient is assigned a personal ID and checks are run on the consistency of their data for date of birth, diagnosis and whether still living. Data that has not been updated every six months is not entered in the reports, but kept as a record on the database. Inconsistent data is signaled to the centers where the patient was observed and the data is deleted if not appropriately corrected. Duplicate entries are recognized by a program that updates all data arriving from the same ID, and which merges records with multiple IDs after running an anonymized check on individual patients' personal details. In the first six months of 2010, the Emocard system was managing 10 297 records, 8 500 of which were of living patients, 567 of deceased patients and of 177 patients whose living status was unconfirmed. The 52 hemophilia treatment centers in Italy are somewhat unevenly distributed geographically. On average, each center manages 163.46 (mean) patients. In the North of the country 3 821 patients are managed by 26 centers (mean: 146.96 patients/center). In the Center of Italy, 1 862 patients are managed by 9 centers (mean: 206.89 patients/center) and in the South and Islands, 2 089 patients are managed by 17 centers (mean: 122.88 patients/center). While the North and Center of the country enjoy a more even distribution of treatment centers, in the South the centers are often clustered (in Campania 3 of the 4 centers present in the region are located in Naples; in Apulia 2 out of the 3 are in Bari, and in Sicily 2 out of 3 are in Palermo). The region with the highest number of centers (nine) is Emilia-Romagna. There is not one single center in the regions of Valle d'Aosta, Molise, or in Basilicata. The region with the highest number of patients per center is Tuscany, with 1 006 patients managed by 2 centers (mean: 503 patients/center), followed by Lombardy (1 345 patients shared by 5 centers; mean 270.8 patients/center) and by Liguria (255 patients with just one center). The region with the lowest number of patients per center is Calabria, with 209 patients managed by 3 centers (mean: 69.67 patients/center), followed by Marche (71 patients with just one center) and by Emilia-Romagna (699 patients shared by 9 centers; mean of 77.67 patients/center). Over the past two years, the Emocard system has been migrating to an online EMOWEB platform, which today is almost fully up and running in Italy's hemophilia centers.

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## 2. Therapeutic management of Hemophilia A

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### INTRODUCTION

Treatment of the hemophilic patient is implemented by means of an infusion of the deficient clotting factor, therefore, in the case of Hemophilia A, of Factor VIII (FVIII) (1).

Here it is necessary to distinguish between acute treatment of the hemophilic patient, with a bleeding episode taking place, and routine treatment, aimed at prevention of sequelae, and characterized by the planned continuous administration of concentrates. In other words, we distinguish between 'on demand' therapy and prophylaxis.

'On-demand' treatment is implemented during a bleeding episode in order to limit its severity and to induce its resolution. It consists in the intravenous administration of the deficient factor and it is the single most important intervention, to the extent that it should be carried out before any closer examination takes place. The dose of FVIII used has to be based on the calculation that each International Unit (IU) administered per kilogram of body weight can increase plasma levels of FVIII by around 2%, and that the half-life of the product is approximately 8-12 hours (2). Complementary to this substitution therapy, analgesics may be used to control pain (3).

Prophylaxis, on the other hand, consists in the continuous administration of the deficient factor and it may be subdivided into primary and secondary prophylaxis (4-6) (Table 1).

Prophylaxis may also be adopted in conjunction with surgery, before and following an intervention or an invasive maneuver in order to prevent bleeding complications. There is also short-term prophylaxis, which is carried out in patients with repeated bleeding, especially if it is in a target joint. This consists in 4-8 weeks of administration of the deficient factor and has as its objective the arresting of the bleeding (2).

The scientific evidence suggests that primary prophylaxis is preferable in managing the hemophilic patient (7, 8), especially in the case of severe hemophilia, even though a debate continues in the literature over whether it is possible to continue with prophylaxis in adult patients (9, 10). The prophylaxis protocol recommended by the World Federation of Hemophilia (WFH) consists in the infusion of 25-40 IU/kg of FVIII three times per week (2). The WFH acknowledges that primary prophylaxis is expensive, but at the same time affirms its long-term cost-effectiveness and efficacy in reducing bleeding episodes and in maintaining joint function (2). This would appear even more pertinent when one considers the possibility of managing the therapy at home. Thanks to specific regional laws, hemophiliacs can be provided independently for the management of the treatment in their own home and without the presence of healthcare personnel. This trend, which aims to dehospitalize management of the disorder, is further favored by the implementation of home-care social assistance. These measures bring benefits both for the quality of the assistance itself and for the allocation of resources (see Chapter 6 on organizational aspects).

The products to be used to ensure this prophylaxis will be dealt with in later chapters, in which we report the available guidelines for the treatment of Hemophilia A in Italy. The guidelines of the Italian Association of Hemophilia Centers clearly indicate that the substitution therapy of choice for congenital clotting factor disorders consists in products based on recombinant DNA, wherever these are available. Only where these are not available should plasma derivatives be used (1). More specifically, in the case of Hemophilia A, recombinant FVIII (rFVIII) represents the product of choice for substitution therapy, even though plasma-derived concentrations are

TABLE 1

NOMENCLATURE FOR PROPHYLAXIS (5, 6)	
Primary prophylaxis	Long-term continuous treatment* begun after the first episode of intra-articular bleeding and before the age of 2 years is reached
Secondary prophylaxis	Long term continuous treatment* which does not fulfill the criteria for primary prophylaxis and was begun after 2 or more episodes of intra-articular bleeding or at an age of over 2 years

\*At least 46 weeks/year

considered to be equally effective, and are now characterized by a high level of safety (1).

In view of possible problems of availability, the guide-lines recommend the gradual introduction of rFVIII in accordance with criteria of priority of need. Patients who have not been previously treated are, and have to be, treated with rFVIII, as are patients who test negative for HCV and HIV. For patients with HIV and HCV infections, on the other hand, the choice of a recombinant product over the continuation of treatment with plasma derivatives has the aim of minimizing the risk of transmission of other infections (1).

Alongside the problem of viral safety, the greatest clinical complication facing substitution therapy using FVIII is the possible development of inhibitory antibodies (11-15). Inhibitors, repressed by anti-FVIII antibodies that inactivate this protein, may develop following treatment with cryoprecipitates or with FVIII concentrates, whether these are plasma-derived or recombinant in origin (15). In daily practice, patients are classified as being at low, moderate or high risk of developing inhibitors. Patients with more than 150 cumulative days of exposure (EDs) are considered to be at low risk, while patients with fewer than 20 cumulative EDs are said to be at high risk. The classification of patients at moderate risk is considered to be difficult and controversial: in practice, the trend is to consider patients with up to 50 cumulative EDs as being at high risk (16).

In addition to this classification, a different approach considers to be at high risk those patients that have a phenotype of severe Hemophilia A and have not been treated previously (Previously Untreated Patients - PUPs), and patients who have fewer than 20 days of exposure to FVIII: these patients require

careful follow-up to monitor any development of inhibitors, above all in the initial phases of treatment. On the other hand, patients who have been treated previously (Previously Treated Patients - PTPs) and those who already have some days of exposure to FVIII are considered to be at low risk.

The appearance of inhibitors in stable patients who have been treated previously, especially in those affected by moderate and mild Hemophilia A, may reflect the presence of neoantigens in FVIII concentrates (15). Recently, the European Medicines Agency (EMA) has arrived at the conclusion that the appearance of inhibitors in PUPs is an immune reaction to an exogenous protein correlated with environmental factors and with factors intrinsic to the patient (the defect of the FVIII coagulation gene, an immune-type genetic predisposition and family background). Contrastingly, the *de novo* development of inhibitors in multi-transfusions and among stable PTPs, where intrinsic risk factors have been ruled out, could reflect neoantigen formation in infused FVIII (16, 17). For this reason, the EMA argues that assessments of the immunogenicity of a specific product should be conducted on this type of stable and previously treated patient and not on patients who have never been exposed to substitution therapy (16).

Although the presence of FVIII inhibitors may not be permanent (15), some may persist and inhibit the activity of this protein, interfering with its link to the complex that activates factor X and thus reducing the efficacy of treatment (12). This major complication may have an important impact both on the efficacy and on the cost of therapy (16-22), even though, fortunately, progress is today being made towards avoiding such consequences, especially through more sophisticated approaches and



TABLE 2

## PRINCIPAL CHARACTERISTICS OF THE PLASMA-DERIVED CONCENTRATES MOST WIDELY USED IN ITALY

PRODUCT (DISTRIBUTOR)	PURIFICATION	VIRAL INACTIVATION	SPECIFIC ACTIVITY* (IU/MG PROTEIN)	REMARKS
Alphanate® (Alpha Therapeutics)	Heparin affinity chromatography	Solv/Deterg + 72 h at 80°C	140	Alb+ vWF +
Beriate P® (CSL Behring)	Ion-exchange chromatography	Pasturization for 10 h at 60°C	165	Alb- vWF -
Emoclot D.I.® (Kedron)	Ion-exchange chromatography	Solv/Deterg + 30' at 100°C	>80	Alb- vWF +
Fanhdi® (Grifols)	Heparin affinity chromatography	Solv/Deterg + 72 h at 80°C	>100	Alb+ vWF +
Haemoclin SDH® (Biotest)	Ion-exchange chromatography	Solv/Deterg + 30' at 100°C	100	Alb- vWF -
Haemate-P® (CSL Behring)	Multiple precipitation	Pasturization for 10 h at 60°C	38	Alb+ vWF +
Talate® (Baxter)	Ion-exchange chromatography	Det. + Steam for 10 h at 60°C	70+30	Alb+ vWF +

\*specific activity before the addition of albumin as a stabilizer

Adapted from Santagostino(1)

through products with lower risk of inhibitor development (23-29).

## PRODUCTS FOR TREATMENT AND PROPHYLAXIS: EFFICACY AND SAFETY

### Plasma derivatives

Plasma derivatives are concentrates of coagulation factors that have been *derived from human plasma* (1). *Products derived from fresh plasma*, that is, from *frozen and cryoprecipitated fresh plasma* (1), which represent the first anti-hemophilia therapy to be made available to the hemophilia community, have been commercially unavailable for some years now and for this reason will not be dealt with here.

*Concentrated plasma derivatives* are obtained from plasma pools gathered from thousands of donors, out of which individual clotting factors are purified using various methods of fractionation, with results that vary in terms of their degree of purity, here to be understood as specific activity per mg of

protein (1). To be more precise, FVIII is initially separated from the plasma by cryoprecipitation and is then further purified using a variety of techniques, on the basis of which three main product groups can be distinguished: FVIII concentrates *having an intermediate degree of purity*, which are obtained using conventional techniques of precipitation-adsorption, concentrates *that have been purified using chromatography*, and concentrates *that have been purified using monoclonal antibodies* (1).

The concentrates of plasma derivatives that are in current use in Italy are shown in Table 2 (1, 30).

The number of FVIII units administered is expressed in IU, the units having been assigned with reference to current International Standards of the World Health Organization (WHO) for human FVIII concentrates (31). Unlike concentrates obtained through affinity chromatography using columns containing monoclonal anti-FVIII antibodies, many of the plasma-derived FVIII concentrates purified using ion exchange chromatography also contain Von Willebrand factor. These formulations have

therefore also been approved for the treatment of Von Willebrand disease as well as for treating hemophilia (30).

## EFFICACY

The efficacy of *plasma-derived concentrates* has been assessed in various studies, separately for each one of the preparations used; unfortunately, for most of these, the assessment relates to their use in patients affected by Von Willebrand disease and only a few to patients affected by Hemophilia A (32-39).

For the only concentrate of intermediate purity, (Haemate-P®), tests of its efficacy derive from its widespread use, since the early 1980s in over 35 countries, for on-demand therapy and long-term prophylaxis with Hemophilia A. Over more than 25 years of clinical experience, the drug has demonstrated excellent hemostatic efficacy in both pediatric and adult patients and it is today used with efficacy also in the treatment of Von Willebrand disease (40).

Other available studies concern Haemoctin SDH® and Talate®: Haemoctin SDH® has been subjected to 3 prospective, uncontrolled, open-label studies on patients with previously treated severe Hemophilia A. From these it emerged that the concentrate is effective in preventing and controlling bleeding episodes, in long-term prophylaxis and in on-demand treatment, even with major interventions such as general surgery or orthopedic surgery (41). The efficacy and safety of the product have also been demonstrated in the study by Zozulia and Pliushch, who suggest that its performance could be increased and patient quality of life could be improved by personalizing the therapeutic approach as much as possible through the appropriate choice of drugs, dosages and regimes (42).

In the case of Talate®, one multi-centric prospective clinical study has been conducted on 56 patients with severe Hemophilia A, who had previously been treated with an older formulation of the product, in order to assess its efficacy in on-demand therapy, in prophylaxis or in both. In this case, too, the efficacy of this concentrate was demonstrated to be equivalent to that of its predecessor but with the difference of having a broader spectrum viral inactivation (using solvent/detergent instead of detergent alone) (43).

## SAFETY

Studies carried on FVIII concentrates derived from cryoprecipitate have shown that there is no viral clearance during the initial phase of precipitation; however, many of the more recent methods for producing FVIII incorporate additional chromatographic phases to remove contaminants, including viruses (44). During a purification phase using chromatographic affinity, immobilized monoclonal antibodies directed against FVIII can be used specifically to capture the factor itself, thus enabling contaminating proteins and small viruses without capsules such as the polio virus, to flow down the affinity column (44-47).

On the other hand, treatment with solvents/detergents can also inactivate encapsulated viruses, such as HIV, and reduce its presence to below detectable levels (44). An even broader safety margin can be obtained if the final containers for some products using frozen FVIII are subjected to dry heat treatment at temperatures of over 80°C for more than 72 hours. This will inactivate HIV and other encapsulated viruses, such as those of hepatitis B and hepatitis C (44).

Many studies have analyzed the safety profiles of plasma-derived concentrates, although these focused more on aspects concerning the risk of infection and less on adverse events in general. The main findings of these studies (41, 43, 48-61) are shown in Table 3.

It can therefore be inferred that the safety of plasma derivatives, in terms of infection risk, is greater today than it was in the past; however, as non-encapsulated viruses such as the Parvovirus B19 or the emergent Parvovirus 4 are resistant to these inactivation processes, it is not possible to claim that these products are completely safe from this point of view (62-64). Furthermore, cases of infections from newly emergent pathogens, not only viral, have been reported, which are potentially a danger to patients. Cases have also been reported of viral infections that have manifested themselves after a long period of latency, sometimes lasting many years (65, 66). Finally, it cannot be asserted that the risk of infection via transmission through prions has been excluded for plasma derivatives, as has been demonstrated in the extremely rare but confirmed cases connected with whole blood transfusions or concentrates of erythrocytes,

TABLE 3

## PRINCIPAL SAFETY ASPECTS OF THE MOST WIDELY USED PLASMA-DERIVED CONCENTRATES

PRODUCT	AVAILABLE STUDIES (YEAR)	INFECTION RISK	ADVERSE EVENTS	DEVELOPMENT OF INHIBITORS
Alphanate® (Alpha Therapeutics)	Diez et al. (2009) (48)	Positive results from new purification processes to reduce prion risk to a minimum	-	-
Emoclot D.I.® (Kedrion)	Tradati et al. (1995) (49)	No clinical signs of hepatitis A nor of antibody development against HAV, HBV, HCV or HIV 1-2 in PUPs observed over 52 weeks	-	-
Fanhdi® (Grifols)	1: Ristol et al. (1996) (50)	1: no infections during clinical experience; no residual infections for encapsulated viruses (HIV, HAV, HBV, HCV) following treatment with solvent/ detergent and freeze-drying; reduction in the infection risk from Parvovirus B19 following heat treatment	No increase in observed risk	
	2: Diez et al. (2009) (48)	2: positive results from new purification processes to reduce prion risk to a minimum		
Haemoclin SDH® (Biotest)	Wolf et al. (2004) (41)			
Hemate-P® (CSL Behring)	1: Schramm et al. (2008) (51)	1: proven efficacy in elimination of HBV, HCV, HIV		
	2: Bentorp et al. (2008) (52) 3: Gröner A. (2008) (53) 4: Schimpf et al. 1987 (54) 5: Schimpf et al. (1989) (55)	2-5: no cases of confirmed viral infection in >600 enrolled patients	2: rare, reported in 1 out of 4 297 single standard doses administered over 16 years of post-marketing observation	
	6: Vey et al. (2001) (56) 7: Schäfer et al. (2006) (57)	6, 7: risk from prions reduced to a minimum through new purification methods		
	8: Lethagen et al. (2007) (58) 9: Makris et al. (2002) (59) 10: Mannucci PM. (2002) (60)		2, 8-10: allergic and anaphylactic reactions reported: fever, hemolysis, thromboembolic complications and hypervolemia	8-10: reported in few cases
Talate® (Baxter)	1: Nemes et al. (2007) (43)		1: non-severe adverse events developed in 41.1% of patients	1: not reported for any of the patients taking part in the study
	2: Bentorp et al. (2001) (61)	2: no signs of viral infection in the 7 patients in the study during the observation period		

which occurred in the United Kingdom (65-67).

In view of these difficulties, in both Western Europe and in the USA, recombinant products are taking over from and will eventually replace plasma derivatives in hemophilia therapy (65, 68).

### Recombinant factors

Recombinant factors have been subdivided into different generations on the basis of their content of human or animal protein in the culture medium or in the final formulation, in accordance with the recommendations of the Medical and Scientific Advisory Council (MASAC) (69). In line with this classification, in what follows we shall consider those products that contain human or animal protein both in the cell culture medium and in the final formulation to be first-generation products. Second-generation products are those that contain such protein only in the culture medium and not in the final formulation and finally third-generation products are those totally free from animal or human protein.

### First-generation recombinant factor VIII products

First generation recombinant factor VIII products (Recombinate®; Baxter Healthcare, Westlake Village, CA and Kogenate®; Bayer Healthcare, Berkeley, CA) entered into clinical practice at the end of the 1980s (70). They included protein of animal origin and of human derivation in their cell cultures, and human albumin was added as a stabilizer to the final formulation (71).

These products were synthesized by inserting human FVIII genes into ovary cells of the Chinese hamster (CHO cells) or into baby hamster kidney cells (BHK cells). In the culture, the CHO cell lines secrete rFVIII factor into the culture medium; subsequently, the rFVIII undergoes a purification process, using a series of chromatography columns.

Production via BHK cells uses a continuous cultivation process which would appear to have the potential of eliminating the risk that enrichment of metabolic products that may appear within the culture medium (72). In this case too, the rFVIII is left within the culture medium and is subsequently gathered, isolated and purified using a combination of ion exchange chromatography, filtration

gel and immunoaffinity chromatography. The synthesized rFVIII has the same biological effects as human FVIII: structurally, the proteins have the complete combination of heavy and light chains, just like native FVIII.

Thanks to technological progress, first-generation recombinant factors are now no longer used in clinical practice; indeed, Kogenate® has been substituted by an analogous second generation product and Recombinate® is no longer marketed.

### EFFICACY AND SAFETY

With regard to the assessment of efficacy, a study by White et al. (73) evaluated 69 patients with Hemophilia A (67 severe and 2 mild) treated at home using rFVIII Recombinate® for prophylaxis or for treatment of bleeding episodes over periods of between 1 and 5.7 years (median value 3.7 years). Response to treatment was categorized as good or excellent in 3 195 (91.2%) of the bleeding episodes; furthermore, 13 patients who used rFVIII for prophylactic treatment showed excellent hemostasis. Out of 13 591 infusions, 13 adverse reactions (0.096%) were reported, none of them severe, while none of the patients developed inhibitors. In another study conducted on 102 patients, 21 of them (20, 6%) did, however, develop inhibitors, of which 19 belonged to the high-risk group (74, 75). In contrast to this, a study conducted on 58 PTP hemophilia sufferers undergoing home-based therapy, found no development of inhibitors (76). Finally, an observational study conducted in Canada on 478 patients concluded that it is possible to estimate a risk of the appearance of inhibitors both before and after the transfer from plasma-derived products to first generation rFVIII (77).

With regard to safety, as previously described, the transmission of pathogens by the hematic route, due to the use of plasma-derived products, has long been foremost among the issues under consideration (66). Recombinant factors were introduced specifically for this reason. They offer clear advantages in safety as they are produced using validated laboratory techniques. The use of plasma-derived materials, which are screened and purified during the fermentation, purification and formulation of rFVIII products, represents a first step in the direction of safety (78). In products based on first generation rFVIII, human protein is,

however, used in the production process and therefore is present at the levels of cell culture, purification and final formulation.

In order to reduce the presence of potential transmissible pathogens to a minimum in this product type, such laboratory techniques are available as ion exchange chromatography or immunoaffinity chromatography using monoclonal antibodies and targeted purification procedures (79).

### Second generation recombinant factor VIII products

The second generation products currently in use in Italy for treating Hemophilia A patients are Kogenate® Bayer and Helixate® Nexgen (CSL Behring). Kogenate® Bayer (octocog alfa), is also available in Italy under the trade name Helixate® Nexgen. It combines the advantages of the full-length human FVIII molecule with an albumin-free synthetic formulation containing sucrose, and with a better viral safety profile than the first generation of recombinants by incorporating an inactivation stage based on the use of solvents/detergents. The product is cultured on BHK and the culture medium contains recombinant human serum albumin; this has led to the attribution of the second-generation epithet according to the MASAC criteria to this recombinant product (69). The purification stage involves viral inactivation that leads to very low levels of contamination in the final product. The product contains sucrose, glycine, histidine and calcium as stabilizers and buffers; it is, however, free of albumin or other excipients of human or animal origin (67).

## EFFICACY AND SAFETY

Four clinical trials have been conducted to assess the clinical efficacy of these factors. Three of these studies (67, 80, 81) were conducted on previously treated patients (PTPs) ( $\geq 100$  exposure days) with a follow-up range of 18 months. The fourth study examined patients who had never previously been treated (PUPs) or who had been exposed to treatment for fewer than 5 exposure days, following them for a period equal to or greater than 2 years (82). The primary endpoint for assessment of efficacy was the number of infusions required to attain hemostasis for each bleeding episode.

A common finding emerged from these trials: that of a high degree of efficacy for these drugs in guaranteeing hemostasis. In fact, 74-82% of the bleeding episodes could be treated with a single infusion, while with one or two doses, hemostasis was guaranteed in 89-95% of cases. Furthermore, subjective judgments of improvement in patient condition were excellent or good for 81-100% of the bleeding episodes.

From the trials conducted on hemophilic patients undergoing surgical interventions, to whom recombinant drugs were continuously infused or administered as a bolus, in 100% of treated cases the surgeon expressed a judgment of good or excellent regarding the use of these drugs (83, 84).

The percentage of adverse events that can be correlated with the infusion of these factors was 0.19% among PTPs and 0.14% among PUPs. The adverse events most commonly encountered were: skin rash/itching, local reactions at the injection site, hyper-sensitivity reactions (e.g. feeling of unsteadiness, nausea, pain/malaise in the chest, and slight drop in blood pressure), altered sense of taste and fever (85).

As has already been highlighted, the best known and most serious complication is the development of inhibitors. According to the findings of the four trials cited above, 15% of PUPs developed inhibitors, while among the PTPs, no patient encountered this adverse event (85). Data from a meta-analysis show a percentage of development of inhibitors of 8.2% among PUPs (86). However, as was reported earlier in this chapter, according to the EMA, PUPs do not represent the most suitable population on whom to assess the risk of developing inhibitors connected to a specific product; on the contrary, it is PTPs that constitute the more relevant population, and the production of inhibitors among this category of low-risk patients would be taken as proof of a product's high level of immunogenicity (16).

### Third-generation recombinant factor VIII products

Among the third-generation clotting factors we find *Advate*®, produced by Baxter and the subject of the present HTA report – for which reason readers are referred to the relevant chapter – and *ReFacto AF*®, which is marketed by Pfizer.

*ReFacto AF*® is an rFVIII that was given the definition of third-generation product as it is free of albumin or other blood or plasma derivatives in each of its production steps. The drug is indicated for the control and prevention of bleeding episodes in patients affected by Hemophilia A and for surgical prophylaxis during minor and major surgery in patients affected by the same disorder (87). The drug is administered intravenously in infusion and is available as a powder preparation in vials containing various dosages (87).

*ReFacto AF*® (morotocog alfa) is a development of *ReFacto*®, a second-generation rFVIII, a variant of the FVIII molecule, which is without its B domain (88, 89). The absence of its B domain would appear to modify the product's efficacy in treatment, probably due to a reduction in the drug's half-life (90). Indeed, a meta-analysis by Gruppo et al. found that there is approximately double the risk of developing bleeding during a prophylactic course of therapy with B-domain-deleted products compared to full-length-molecule products, when dosage and age are held constant (90). Apart from the influence of the drug's half-life, this finding could also be explained by the role potentially played by the B fragment during the activation phases of the coagulation cascade, binding of platelets, proteolytic inactivation and clearance (91-93). It should, however, be said that the meta-analysis by Gruppo et al. has been subjected to a series of criticisms. These focus in the main on the methods chosen for the process of estimating data and on the comparability of the patient groups (94, 95). Other studies do exist that substantiate the bioequivalence of B-domain-deleted products with those having the full-length molecule (96-98).

*ReFacto AF*® is produced through cultivation in a CHO cell line. Human albumin has been eliminated from the culture medium during the production process of *ReFacto AF*®. In addition, during the purification phase, monoclonal antibodies with synthetic peptides have been added. An extra filter is used for larger-sized viruses such as retroviruses. These changes have not had any noticeable effects on the product's structural integrity, nor on its clinical efficacy (99).

## EFFICACY AND SAFETY

A phase-3 pharmacological study of 94 patients affected by Hemophilia A, who had

previously been treated with rFVIII, assessed the efficacy and safety of  $30 \pm 5$  IU/kg of *ReFacto AF*® administered on demand and for prophylaxis of bleeding episodes (three times per week) (100). Of the 94 patients, 6 had their prescribed dosage of the drug increased during the course of the study and 43 did not report any bleeding during treatment (45.7%). In the light of these findings, during the authorization procedure, the EMA considered it worthwhile, in the Summary of Product Characteristics (SPC) for *ReFactoAF*®, to re-state the warning that had already been issued for *ReFacto*® concerning the occurrence of episodes of non-efficacy with the product, mainly with patients treated in prophylaxis (101).

Another study set out to analyze the efficacy of *ReFacto AF*® in prophylaxis during major surgery on 22 patients affected with Hemophilia A. They were administered rFVIII instead of their usual therapy over at least 6 days starting from the immediate post-operative period. In 13 patients, post-operative bleeding was encountered, but for 10 of these, this was considered normal (102).

The most commonly reported adverse reactions to treatment were headaches (24% of patients), nausea (6%), diarrhea (5%), asthenia (5%) and hyperpyrexia (5%), all mild or moderate in severity (100). Of the 89 patients, 2, who were exposed to the treatment for over 50 days, developed inhibitory antibodies (2.2%) in this study by Recht et al (100).

In a work by Windyga et al, the most common adverse reactions found to treatment were: hyperpyrexia (41% of patients), headaches (9%), nausea (9%), diarrhea (5%), vomiting (5%) and asthenia (5%), all mild or moderate in degree (102).

No data is available on the development of inhibitory antibodies among previously untreated patients (PUPs), but clinical trials are planned. In the undesirable side effects section of the summary of product characteristics, for *ReFacto AF*®, there is, however, a note about the high percentage of previously untreated patients (32%) who developed inhibitory antibodies when treated with the old *ReFacto*® product (101).

## Management of patients with inhibitors

As has been pointed out previously, one of the main problems with treatment using

coagulation factors is the development of inhibitors, which are capable of neutralizing the therapeutic action of the treatment.

The prevalence of anti-FVIII inhibitors varies in the literature, between 5% and 7% (21), although in the cases of severe and moderate Hemophilia A it may reach values of between 7% and 18% (103) with a peak of 30% among patients affected by severe hemophilia (104). The risk of developing inhibitors is greater during first exposures: this indicates the necessity for frequent monitoring of the patient, starting from the initial infusion (105). The cumulative risk of developing inhibitors varies, according to various studies, between 0% and 39%. The risk depends on previous exposure to treatment, the severity of the disease and on the type of product used (21). A meta-analysis conducted by di Iorio et al. has demonstrated that the risk of developing an inhibitor is 14.3% among PUPs, when using plasma-derived products, and 27.4% when using recombinant products, with the highest percentages among patients with severe hemophilia (106). This meta-analysis also showed that the risk reduces when high-purity plasma derivatives are used, when compared to products of intermediate purity (10.2% vs. 15.9%) (106).

From the clinical point of view, as has often been stated, inhibitors represent the most serious of all complications. Their presence renders treatment of bleeding episodes more difficult and increases the risk of uncontrollable bleeding and disability, and especially of arthropathy (107-109). The clinical difficulties of managing this complication entail the extremely high consumption of resources both to eradicate the inhibitor itself and to resolve the bleedings.

In treating acute bleeding episodes in patients who have developed inhibitors, the therapeutic approach may be to make use of high concentrations of FVIII, of concentrated activated prothrombin complex (*FEIBA*®) or of activated recombinant factor VII (*Novoseven*®) (110-114). The choice for the treatment of bleeding episodes in patients with inhibitors is made according to the severity of the episode, the titer of inhibitor present at the time of the episode and the anamnestic response, by which is meant the increase in levels of inhibitory antibodies induced by exposure to FVIII concentrates or other hemoderivatives which contain minimal quantities of these agents. Patients with an anamnestic response

of above 5 Bethesda Units (BU)/ml are defined 'high responders'; all the others are termed 'low responders' (105).

In the event of a severe, life-threatening bleeding episode, or one that endangers the functioning of the musculo-skeletal system, low responders may be placed under substitution treatment using human plasma-derived or recombinant FVIII at high dosages (115, 116). The recommended dosage is based on an initial administration of a neutralizing dose (titer of inhibitor per plasma volume) and an incremental therapy (20-50 IU/kg of body weight), followed by maintenance doses, repeated at regular intervals or administered by continuous infusion, aimed at reaching and maintaining the pre-selected plasma levels (the same incremental dose repeated every 6-8-12 hours). If repeated, this treatment can also induce a 'spontaneous immune tolerance', with disappearance of the inhibitor (117). In the event of no therapeutic response, other options consist in activated recombinant FVII or activated prothrombin complex, the so-called 'bypassing agents' (105).

Among high-responder patients, choice of treatment is based on these bypassing agents, i.e., on activated recombinant FVII and on activated prothrombin complex (118-122). An extreme therapeutic option consists in extra-corporeal immunoadsorption with staphylococcal A protein aimed at reducing the inhibitor titer to levels of 5-10 BU/ml, compatible with its neutralization using FVIII, possibly in association with immunosuppressants (cyclophosphamid) and/or high doses of intravenous immunoglobulin (123).

The induction of immunotolerance (ITI) is today the only known method capable of reducing or even eradicating anti-FVIII inhibitors (105, 124, 125).

ITI is based on the repeated administration of high doses of FVIII over a long time period, in accordance with a variety of regimes (Table 4) (126-131), and with a percentage of success varying between 60% and 80% (105, 132).

A recent study carried out to assess responses to ITI using *Advate* in 12 children showed a percentage of success of 75% across the entire sample and of 70% in 10 high-responding patients (133). This demonstrates that results attainable with *Advate* are in line with those in the international scientific literature.

The presence of a concentration of inhibitor of below 10 BU/ml before initiation of ITI,

TABLE 4

ITT REGIMES		
PROTOCOL	TYPE OF TREATMENT	REFERENCES
Van Creveld	Phase 1 – FVIII 25-50 IU/kg twice daily for 1-2 weeks Phase 2 - FVIII 25 IU/kg daily 2-3 times per week	(126)
Bonn	First phase: FVIII 100 IU/kg and APCC 50 U/kg twice daily Second phase: FVIII 150 IU/kg twice daily	(127)
Malmö	Immunoabsorption with protein A until titer is < 10 BU/ml High doses of FVIII, subsequently every 8-12 hours to keep levels > 30% IVIg 2.5-5 g on day 1 and 0.4 g/kg per day on days 4 and 5 cyclophosphamid: 12-15 mg/kg iv (days 1-2); 2-3 mg/kg by mouth (days 3-10)	(128, 129)
Kasper	FVIII 50 IU/kg per day and prednisone by mouth	(130)
Gruppo	FVIII 100 IU/kg per week, IVIg, cyclophosphamid, prednisone	(131)

IVIg: intravenous immunoglobulin; APCC: activated prothrombin complex concentrate

along with a maximum historic peak below 500 BU/ml and an early start of treatment, represent positive prognostic factors for the success of ITI (134-138).

There is, however, conflicting evidence regarding the dose/effect ratio (125,139), although there is consensus that treatment should begin within 12 months of diagnosis and with a titer of inhibitor below 10 BU/ml. Treatment should continue until the disappearance of the inhibitor and the normalization of in vivo recovery of the half-life of infused FVIII (105).

Given its complexity, the treatment of patients with inhibitors nevertheless demands that they are referred to hemophilia centers with the highest levels of specialization and experience (105).

## CONCLUSION

Treatment of patients with Hemophilia A is implemented through the infusion of the deficient clotting factor, i.e. of factor VIII. Therapy may be conducted on demand, during a bleeding episode, in order to limit its severity and to induce a resolution, or it may be prophylactic, aimed at reducing the risk of joint

damage. Primary prophylaxis, in particular, constitutes the gold standard for prevention of articular degeneration, as established by the World Federation of Hemophilia (WFH).

As is also stated in the guidelines of the Italian Association of Hemophilia Centers, substitution treatment should be implemented using recombinant-DNA products whenever these are available. Plasma-derived FVIII presents potential safety issues, which should be borne in mind, not so much because of the 'historic' infections (HIV, HCV, HBV), which became so widespread during the 1980s, but rather because of the risks of infection from as yet unknown pathogens or those which are difficult to control.

Recombinant factors are obtained using recombinant DNA technology and they are subdivided into first-, second- and third-generation products, according to the presence of plasma-derived human or animal protein as additives to the culture medium and/or as stabilizers.

In Italy the products shown in Table 5 are currently available. From the point of view of efficacy, all these products show a good profile, although clearly a higher level of safety from infection could be obtained with those of the most recent generation.



TABLE 5

## CHARACTERISTICS OF PRODUCTS AVAILABLE IN ITALY

	KOGENATE BAYER/ HELIXATE NEXGEN	REFACTO AF	ADVATE
Molecule	Full-length	B-deleted	Full-length
Generation	Second	Third	Third
Cell line	Baby hamster kidney cells	Chinese hamster ovary cells	Chinese hamster ovary cells
Additives in culture medium	Human serum albumin	Plasma-free and albumin-free	Plasma-free and albumin-free
Purification process	Ion-exchange and immunoaffinity chromatography solvent/detergent ultrafiltration	Ion-exchange and immunoaffinity chromatography solvent/detergent nanofiltration	Ion-exchange and immunoaffinity chromatography solvent/detergent
Stabilizer	Albumin-free	Albumin-free	Albumin-free

Modified from Frampton (85)

Furthermore, evidence exists to suggest that the elimination of the B domain from the FVIII molecule, which has been effected in some of the available recombinant products, may influence the clinical effects of the product (89, 140-142).

There remains, however, the issue of the development of inhibitors, the most serious clinical complication of substitution therapy,

due to its dramatic impact both on management and on the resources consumption.

Finally, given the complexity of this disorder, each Company should investigate the possibility of enriching the therapeutic options through initiatives aimed at adding value to individual products as a part of overall patient management.

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### 3. Resources deployed by the National Health Service in Italy and related costs of managing Hemophilia A

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The present chapter will describe the costs of managing hemophilic patients. Data sources used are the scientific literature, current data bases and national charge scales. The international and national literature on the costs of the disorder will be reviewed and an analysis of the costs relating to diagnostic examinations and pharmaceutical treatment for Hemophilia A will be conducted. Finally the rates of hospital discharges for Hemophilia A will be calculated and an estimate made of the direct costs to the National Healthcare System (the Italian SSN) that due to hemophilic patients.

#### REVIEW OF THE INTERNATIONAL AND NATIONAL LITERATURE ON THE COSTS OF HEMOPHILIA A

This review was carried out by researching the scientific literature on the consumption of resources for Hemophilia A. The electronic databases of PubMed and Ovid were queried with the following search term: *haemophilia A and (costs OR economic)*. For an overview of the epidemiology, nosology and clinical aspects of the disease, see Chapter 2.

For people who suffer from hemophilia, the bleeding and related joint complications often lead to disability and to a deterioration of their quality of life (1). Management of hemophilic patients has improved over the years thanks to the introduction of treatments that are safer in terms of the transmission of blood-borne pathogens. Nonetheless, the complex nature of this disease means that there is considerable consumption of both financial and human resources (2-4).

Aledort states that, although the disease has a low prevalence, Hemophilia A absorbs a great quantity of resources, particularly for

substitution therapy using blood clotting factors (5), and these resources become even more substantial when patients affected by severe Hemophilia A develop inhibitory antibodies (6). Against this, Bohn and colleagues (7) argue that there is no statistically significant difference in the median number of hospitalizations between patients with and those without inhibitors. On the other hand, the European Study on Orthopaedic Status (ESOS) demonstrated a significant difference in terms of the levels of arthropathy among young persons (14-35 years) with inhibitors compared to those without. It found an increase in the need for orthopedic procedures and a higher rate of hospitalizations for bleeding episodes and musculo-skeletal problems (8).

With regard to the daily costs of hospitalization, in a study by Gautier et al. (9) these costs were found to be five times as high for patients with inhibitors as for those not affected by this problem.

According to a study by Battaglia et al. (10), in Italy in 1993, with the arrival of recombinant products, a patient with severe Hemophilia A could entail annual costs varying, according to the frequency of bleeding episodes, from €64 000 to €138 000, of which 96-97% was attributable to the costs of pharmacological treatment.

Currently, most of the data relating to hemophilia derives from short-term retrospective studies, which offer an analysis of direct healthcare costs only (11). Most of these studies were conducted in individual centers and focused exclusively on drug costs (4, 6). Some studies have demonstrated that over 70% of costs for the treatment of Hemophilia are due to the infusion of factor VIII (12). For example, in 1995, Globe et al. (13) estimated an annual cost of \$139 000 for the treatment

of hemophilia; of that figure, the infusion of factor VIII proved to be responsible for 72% of the total costs. This proportion varied from 45% for patients with mild hemophilia to 83% for severe patients. In other studies conducted in the United States, treatment costs varied from \$65 000 (14) up to \$92 000 (15). According to Schramm et al., in Europe mean unit costs of factor VIII infusion vary from €1 833 in the United Kingdom to €11 300 in Italy (4).

In order to compute overall costs, a 2003 study by Globe et al. (12) used the Medicare costs chart to consider specialist and non-specialist out-patient visits, radio-diagnosis, laboratory diagnostic examinations, psychological assistance, hospital stays and drugs used during the period of reference (13). Total cost of treatment for an individual patient during the reference period was calculated as the sum of costs for all the item categories considered.

Mean annual costs thus estimated for an adult without arthropathy, co-morbidity, free of inhibitors and/or HIV seropositivity came out at \$18 980 for mild or moderate Hemophilia And \$69 656 for severe hemophilia.

A review conducted by Di Minno et al. (11) traced only two prospective studies. A study by Ullman (16) compared healthcare expenses sustained for patients with and without inhibitors, analyzing data gathered over a two-year period from a prospective cohort. Total mean annual costs of patient care for patients with inhibitors were equal to \$340 013. Costs for patients with severe hemophilia that were treated on demand were equal to \$116 058 and costs for patients in prophylactic care were \$152 133.

The authors concluded that, although the use of out-patient substitution therapy was not significantly higher or more expensive for patients with inhibitors, hospital-related expenses for their management increase total costs considerably.

The Cost of Care Inhibitors Study (COCIS) (17), a longitudinal multi-centric prospective study focusing on the costs of the disorder and on the quality of life of hemophilic patients in eleven participating Hemophilia Centers (HCs), enrolled 52 patients with inhibitors aged over 14 years. The study calculated direct costs, multiplying the resources used by unit cost. The direct costs considered were those relating to treatment of the disorder, hospitalization due to bleeding, laboratory examinations, other diagnostic examinations, surgical interventions, rehabilitation and visits by

specialists. Hospitalization costs were estimated by applying the tariffs of the Diagnosis Related Group (DRG) set up by the Ministerial Decree of 1994 (18). In all, there were 397 DRGs for cases where the hospitalization was caused by bleeding episodes or by other hemophilia-related causes, and 209 DRGs for cases of hospitalization for prosthetic joint surgery. In order to calculate the costs attributable to physiotherapy and medical visits at the HCs, the tariffs of the Ministerial Decree of 1996 were applied (19). Also considered in this study were costs relating to less invasive surgery, such as dental and ophthalmic interventions. For each patient, an overall monthly cost of €17 935.10 was estimated. Approximately 60% of the patients incurred a monthly cost of less than €10 000, while 15% generated costs of over €50 000.

Schramm et al. (4) carried out a multi-centric cross-sectional study of 1 042 patients in 18 European area countries (Germany, United Kingdom, Italy, France, Spain, Netherlands, Switzerland, Sweden, Greece and Israel), also with the aim of assessing consumption of health-care resources. For the six countries involved in the study for whom cost data were available (France, Germany, Italy, Sweden and the United Kingdom), medical expenses incurred in the management of patients in substitution treatment with factor VIII were compared. Unit costs were obtained by taking into consideration hospital stays, (including stays in intensive therapy units), visits to HCs and to the general practitioner and the number of units of clotting factor administered. Table 1 shows the unit costs for the six countries concerned.

Negrini et al. (20) conducted a review of the literature concerning costs and outcomes of the various therapeutic approaches used for hemophilic patients with inhibitors. Six of the ten studies traced by the authors considered only patients affected by Hemophilia A with FVIII inhibitors. For example, studies in France by Goudemand (6) demonstrated that there were no substantial differences in costs attributable to low-responder patients with and without inhibitors, while costs attributable to high-responder patients were greater. During the period 1996-1998, mean annual costs per patient were \$60 000 for patients without inhibitor, \$54 000 for low-responders and \$186 000 for high-responders. From the studies analyzed in the review by Negrini et al. (20) it emerges that the treatment of hemophilic patients with



TABLE 1

UNIT COSTS FOR CARE OF HEMOPHILIACS IN SOME COUNTRIES						
MEAN ANNUAL COSTS (PER YEAR)	FRANCE	GERMANY	ITALY	NETHERLANDS	SWEDEN	UNITED KINGDOM
	Prophylaxis (n=6)	Prophylaxis (n=103)	Prophylaxis (n=1)	Prophylaxis (n=55)	Prophylaxis (n=86)	Prophylaxis (n=75)
	On-demand (n=79)	On-demand (n=172)	On-demand (n=70)	On-demand (n=37)	On-demand (n=26)	On-demand (n=128)
Hospital costs						
Prophylaxis	5 960	336	0	1 062	283	429
On-demand	2 213	968	1 683	2 654	63	535
Visits to HCs						
Prophylaxis	41	91	0	-	473	316
On-demand	46	80	38	-	306	181
Specialist visits						
Prophylaxis	17	20	47	5	13	21
On-demand	39	20	4	11	30	9
Factor VIII						
Prophylaxis	6 831	1 962	11 300	-	2 579	1 833
On-demand	1 149	977	1 015	-	503	429

Modified from Schramm (4)

inhibitors involves the highest costs of disease for any chronic disorder. Furthermore, the greatest burden comes from high-responders. Unfortunately, it is not possible to make a comparison of the different therapeutic experiences due to the diversity of the patients under study, their low numbers and the different periods analyzed. Negrini et al. conclude their study stating that an analysis of a greater number of cases, or of national or international coagulation disease registers, could help determine the characteristics of patients who incur the highest costs, so that services may be optimized.

An assessment of the resources deployed by the National Healthcare System (the Italian SSN) in managing patients with HIV and/or HCV comes from a study by Tencer et al. (21), who assessed the use of resources in the healthcare of adult hemophilic patients with and without HIV and HCV infections for the year 2004. For patients with hemophilia only, the mean annual cost was estimated at \$90 942; for hemophiliacs with HIV, the cost was \$108

862; for hemophiliacs with HCV it was \$104 404, and for hemophilic patients with both HIV and HCV the cost was \$144 462. The authors state that the concomitant presence of HIV and HCV in hemophiliacs leads to annual costs that are 59% higher (95% CIs: 34.8%-82.9%) than those associated with patients affected by Hemophilia alone.

#### Indirect costs associated with hemophilia

The few studies that have assessed indirect costs have compared costs associated with the management of patients treated prophylactically with those treated on demand.

The multi-centric study by Schramm et al. (4) assessed indirect costs in the participating countries in terms of lost working days. For prophylactic treatment (Table 2), the United Kingdom, with €994, is the country registering the greatest indirect costs, while for on-demand treatment, Germany is the highest with €961.

As part of a cost-effectiveness analysis

TABLE 2

## MEAN INDIRECT UNIT COSTS (IN EUROS) FOR CARE OF HEMOPHILIACS IN SOME COUNTRIES

COUNTRY	PROPHYLAXIS	ON-DEMAND
France	919	410
Germany	252	961
Italy	0	445
Netherlands	-	-
Sweden	381	51
United Kingdom	994	310

Modified from Schramm (4)

of children affected by severe Hemophilia A, Risebrough et al. (22) estimated indirect costs expressed in terms of working days lost to parents which were a mean of 2 days per parent for each bleeding episode. This study illustrates how prophylaxis brings about a significant saving in resources (\$33 941 on-demand versus \$1 960 for standard prophylaxis), a result that was confirmed by a study conducted by Lippert et al. (23).

In a study by Molho et al. (24) it was estimated that out of 116 patients with severe Hemophilia A or B (82.8% Hemophilia A), 44.8% of patients presented a mean total absence from school of 15.3 days (assessed in the 12 preceding months), while 27.6% of patients registered a mean total of 31.6 working days lost. The mean cost attributable to loss of productivity, calculated on 29 active patients, was of \$791 per year.

Carlsson et al. (25) assessed the indirect costs associated with on-demand and prophylactic treatment in a cohort of patients in Sweden and Norway with severe Hemophilia A and B, who were treated during the period 1989-1999. In this study, indirect costs were calculated through the human capital method, which involved evaluation of the number of working days lost. In this case too, a higher loss of productivity was apparent among hemophiliacs treated on demand (€31 096) compared to those treated in prophylaxis (€13 004).

In the same way, it can be seen from a study conducted in Great Britain by Miners et al. (26), how on-demand treatment brings about a greater average loss of annual productivity (£7 167 on-demand versus £1 007 prophylaxis). In Italy,

Tagliaferri et al. (27) estimated in 84 hemophilic patients with frequent bleeding episodes, that the transfer from on-demand treatment to secondary prophylaxis, leads, through a reduction in the frequency of joint bleeding, to fewer days of absence from school/work (33.9 on-demand versus 1.3 in prophylaxis). However, this study did not quantify the costs associated with the loss of productivity.

In conclusion, from the analyses on the subject presented, it emerges how prophylactic treatment of hemophilia enables absences from school/work to be reduced significantly and as a consequence reduces the indirect costs associated with them.

#### Use of resources: overview

Hemophilia is a disorder as complex as it is rare and it brings with it not just the problems connected with treating the bleeding, but also complications generated by the treatments themselves: the development of inhibitors and, in the recent past, of HIV and HCV infections. In addition, despite being a rare disease, hemophilia entails a high social impact. In the current chapter it is important to report the psychological trauma suffered by hemophilic children, who have to undergo continuous treatment, followed by lifelong periodic administration of injections, and how such a plight conditions their quality of life.

Of similar impact are the costs associated with managing this chronic disorder. The complexity of managing hemophilia in itself absorbs a large quantity of resources.

TABLE 3

## TARIFFS OF DIAGNOSTIC SERVICES (EURO 2010)

CODE	DESCRIPTION	TARIFF (€)	TOTAL (€)
90.76.1	Partial thromboplastin time (PTT)	2.51	8 300.57
90.75.4	Prothrombin time (PT)	2.61	8 631.27
90.62.2	Full hemochrome	4.75	15 708.25
99.06.1	Infusion of clotting factors	11.85	39 187.95
Total			71 828.04

Modified from the Italian Ministry of Health (31)

According to data published by the National Registry of Congenital Coagulation Diseases, in Italy the number of males affected by Hemophilia A totals 3 307 (see Chapter 1). The treatment of hemophilia through the intravenous administration of concentrates of the deficient factor VIII can be effected using one of two distinct approaches (20):

- prophylactic (primary and secondary)
- therapeutic (on demand)

The introduction, over recent years, of factor VIII concentrates obtained using recombinant DNA technology has contributed to an increase in the number of safe alternative therapies available and introduced the possibility of using primary prophylaxis, which offers patients a better quality of life (see Chapter 6), in that it reduces the number of hospitalizations and emergency treatments. There has been a shift from a mode of treatment consisting in the infusion of factor VIII concentrates derived from human plasma - which exposed hemophilia sufferers to a high risk of the transmission of blood-borne pathogens, to the use of factor VIII concentrates obtained through recombinant technology, which are therefore free of viral risk.

#### Quantification of resources deployed and attribution of direct healthcare costs

In the present section, the costs of hemophilia have been calculated from the standpoint of National Healthcare System (the Italian SSN). In order to calculate the direct costs in terms of deployed medical resources, the following items were considered:

- diagnosis and laboratory examinations
- drugs

- hospitalizations
- other costs

To calculate hospital-related costs, DRG tariff scales were taken as cost proxies.

#### Diagnosis

The most commonly used diagnostic laboratory tests are: partial thromboplastin time (PTT) or activated partial thromboplastin time (APTT) and thromboplastin time (PT) (28). Confirmation of hemophilia type is then given on the basis of the dosages of the deficient plasmatic proteins, with factor VIII for Hemophilia A or factor IX for hemophilia B (29).

Tariffs were derived from the Ministerial Decree of September 12 2006 and subsequently adjusted for inflation, using the consumer price index (30). Tariffs were then multiplied by the total number of male hemophiliacs (3 307 in 2008) (Table 3). The mean annual cost of diagnosis per patient obtained was €21.72.

#### Spending on drugs

According to the data published in the OsMed 2009 Report (32), overall spending on hematopoietic drugs for blood and organ treatment totaled €1 775 million, of which more than 50% was met by public institutions with €960 million, while spending on class-A drugs by the National Healthcare System (the Italian SSN) made up €648 million (36.5%) of the total.

At a local level, coagulation factors represent spending of less than 0.05 DDD/1 000 inhabitants/day (DDD = Defined Daily Dose). This can be ascribed to the fact that, as these latter

TABLE 4

EFFECTS OF CONSUMPTION, PRICES AND 'MIX' ON VARIATION IN LOCAL SPENDING ON CLASS-A DRUGS (2008 VS 2009) OF THE NATIONAL HEALTHCARE SYSTEM (THE ITALIAN SSN) FOR ATC B LEVEL

SUB-GROUPS	PRO-CAPITA SPENDING (€)	DDD/1 000 INHABITANTS/DAY	Δ % 2008-2009				Δ % AVERAGE DDD COST
			SPENDING	DDD	PRICES	MIX	
Low molecular-weight heparin	4.0	4.0	6.9	9.0	-0.4	-1.5	-1.9
Antiplatelet drugs excluding clopidogrel	2.3	60.6	0.6	2.9	-2.2	-0.1	-2.3
Clotting factors	1.2	0.0	-26.1	-21.9	0.1	-5.6	-5.5
Epoietin	0.8	0.2	-17.4	-18.5	-0.1	1.4	1.3
Clopidogrel	0.7	0.9	6.9	11.5	-4.2	0.0	-4.2
Antianemic drugs	0.5	15.1	18.3	6.4	8.6	2.4	11.2
Albumin	0.4	0.0	-1.9	0.1	0.1	-2.1	-2.0
Fondaparinux	0.3	0.1	53.2	53.3	-0.1	0.1	0.0
Oral anticoagulants	0.2	5.8	3.3	3.3	0.0	-0.2	-0.1
Infusion solutions	0.2	0.3	-4.4	1.9	-6.7	0.5	-6.2
Heparin	0.1	0.2	-25.0	-22.6	-4.8	1.8	-3.1
Others	0.1	0.3	-7.1	-17.1	-1.2	13.5	12.1
B- hematopoieic blood and organs	10.8	87.5	-1.5	3.7	-0.7	-4.4	-5.1

Modified from OsMed (32)

drugs are covered by the Local Hospital Codex (PHT), they are distributed directly via on-account distribution. Given the high costs of clotting factors, gross per capita spending on a local level (€1.2) is higher by about half again compared to spending on antiplatelet drugs (excluding clopidogrel), despite the considerable differences in levels of consumption (Table 4). Of the active substances belonging to this category, factor VIII produced using DNA recombinant technology (€0.8 pro capita), involves the greatest outlay of healthcare resources.

The year 2009 saw a drop both in spending and in consumption, which was due to a shift towards direct distribution of the more expensive molecules, as with factor VIII used in Hemophilia A therapy (Tables 5 and 6) (32).

As has been highlighted previously, in the case of Hemophilia A, drugs constitute one of the main cost factors, especially in view of the fact that this disorder requires lifelong treatment.

Finally, an estimate was made of the annual

costs for patients treated only prophylactically, which represents the desirable scenario. For a comparison of the costs associated with prophylactic treatment against those associated with on-demand treatment, which is the most widespread treatment type at present, the reader is referred to the section on economic assessment (see Chapter 5).

With reference to the individual medicinal products used in the prophylactic treatment of hemophilia, (see also Chapter 2), Table 7 shows details of the ex-factory prices of the main therapeutic alternatives available. The values have been extrapolated from the resolutions of AIFA (the Italian Medicines Agency) as published in the Official Gazette (33-36). With regard to drugs that have different packaging formats according to quantity of drug contained in each package in terms of International Units (IU), the ex-factory characteristics and tariffs for those packages with the highest number of IUs are given, with their relative unit costs (updated to 2010). Following this, the annual

TABLE 5

GROSS PRO CAPITA SPENDING AND CONSUMPTION IN 2009 FOR DRUGS DISTRIBUTED BY PUBLIC INSTITUTIONS: THE PRINCIPAL, MOST-COMMONLY PRESCRIBED ACTIVE SUBSTANCES FOR ATC LEVEL B (UP TO 75% OF EXPENSES)

THERAPEUTIC CATEGORY AND SUBSTANCES	GROSS PRO-CAPITA SPENDING (€)	%	DDD/1 000 INHABITANTS/DAY	%
Epoetin alpha	2.44	15.3	1.0	3.4
Darbepoetin alpha	2.14	13.4	0.8	2.5
Epoetin beta	1.68	10.5	0.7	2.3
Coagulation factor VIII of human blood DNAr	1.44	9.0	0.0	0.0
Clopidogrel	0.95	6.0	1.9	6.1
Activated eptacog alpha	0.79	4.9	0.0	0.0
Enoxaparin sodium	0.73	4.6	2.5	7.9
Sodium chloride	0.61	3.8	14.9	48.1
Moroctocogum alfa	0.58	3.6	0.0	0.0
Nonacog alfa	0.38	2.4	0.0	0.0
Human albumin solution	0.30	1.9	0.0	0.0
B - Hematopoietic blood and organs	15.99		31.0	

Modified from OsMed (32)

TABLE 6

GROSS PRO CAPITA SPENDING IN 2009 ON DRUGS DISTRIBUTED DIRECTLY: SUBSTANCES FOR ATC LEVEL B (WITH SPENDING OF OVER € 10 MILLION)

THERAPEUTIC CATEGORY AND SUBSTANCES	GROSS PRO-CAPITA SPENDING (€)	%
Coagulation factor VIII of human blood DNAr	1.62	24.5
Epoetin alpha	1.02	15.5
Darbepoetin alpha	0.93	14.1
Epoetin beta	0.72	10.9
Moroctocogum alfa	0.39	5.9
Activated eptacog alpha	0.29	4.4
Nonacog alfa	0.29	4.3
Clopidogrel	0.26	3.9
Coagulation factor VIII of freeze-dried human blood	0.18	2.7
Enoxaparin sodium	0.17	2.6
B - Hematopoietic blood and organs	6.61	

Modified from OsMed (32)

costs of the prophylactic therapy cycle are calculated for an adult male (mean weight 70 kg), undergoing infusions of factor VIII concentrate three times per week.

As drug dosages vary with the severity of the hemophilia, it was decided to report the range of variation of costs (minimum and maximum dosages of IUs per kg), as is

recommended in the Pharmaceutical Handbook (37). For this cost item only, the annual cost has been estimated of a prophylactic therapy cycle for a child/adolescent of 0-18 years (mean weight 30 Kg) undergoing infusions of factor VIII concentrate three times a week.

It can be seen from Table 7 how drugs containing latest-generation recombinant

TABLE 7

## DRUG TREATMENT: ANNUAL COSTS PER PATIENT (EURO 2010)

ATC	DRUG	ACTIVE SUBSTANCE	PRODUCT TYPE	SSN REGIME	EX-FACTORY PRICE (€)	UNIT COST (€)/ IU	ANNUAL COST (€) OF THERAPY (MIN. DOSE IU/KG)	ANNUAL COST (€) OF THERAPY (MAX. DOSE IU/ KG)	ANNUAL COST (€) OF THERAPY (MIN. DOSE IU/ KG)	ANNUAL COST (€) OF THERAPY (MAX. DOSE IU/ KG)
							ADULT		CHILD/ADOLESCENT	
Bo2BD02	ADVATE FL 3000IU+FL SOLV 5ML	Coagulation factor VIII of genetically engineered human blood	Third generation	Payment exempt	2 250.00	0.75	204 750	327 600	87 750	140 400
Bo2BD02	ALPHANATE INF 1F 1500IU+F 10ML + SIR	Coagulation factor VIII of human blood from plasma fractionation	Plasma derivate	Payment exempt	701.52	0.47	128 310	205 296	54 990	87 984
Bo2BD02	BERIATE P 1000IU+SOLV+SET	Coagulation factor VIII of human blood, freeze-dried	Plasma derivate	Payment exempt	380.62	0.38	103 740	165 984	44 460	71 136
Bo2BD02	EMOCLOT FL 1000IU+FL 10ML+SET	Coagulation factor VIII of human blood, freeze-dried	Plasma derivate	Payment exempt	467.70	0.47	128 310	205 296	54 990	87 984
Bo2BD02	FANHDI INF FL1000IU+SIR PRER. SOLV.	Coagulation factor VIII of human blood, freeze-dried	Plasma derivate	Payment exempt	467.60	0.47	128 310	205 296	54 990	87 984
Bo2BD02	HAEMATE P 1000 IU+FL30 MLSET	Human Coagulation Factor VIII	Plasma derivate	Payment exempt	465.38	0.47	128 310	205 296	54 990	87 984
Bo2BD02	HAEMOCTIN FL 1000IU+FL 10ML+SI	Coagulation factor VIII of human blood from plasma fractionation	Plasma derivate	Payment exempt	467.60	0.47	128 310	205 296	54 990	87 984
Bo2BD02	HELIXATE NEXGEN 2000IU+1FL+KIT	Coagulation factor VIII of genetically engineered human blood	Second generation	Payment exempt	1 373.76	0.69	188 370	301 392	80 730	129 168
Bo2BD02	KOGENATE BAY- ER FL 2000IU+SIR PRER. SOLV. 5ML +SET	Coagulation factor VIII of genetically engineered human blood	Second generation	Payment exempt	1 373.76	0.69	188 370	301 392	80 730	129 168
Bo2BD02	TALATE FL 1000IU+ FL 5ML+SIR	Coagulation factor VIII of human blood, freeze-dried	Plasma derivate	Payment exempt	413.78	0.41	111 930	179 088	47 970	76 752
Bo2BD02	REFACTO AF 1FL 2000IU+ SIR. PRER. SOLV. 4ML	Coagulation factor VIII of genetically engineered human blood	Third generation	Payment exempt	1 373.76	0.69	188 370	301 392	80 730	129 168

TABLE 8

## MEAN ANNUAL PER-PATIENT COST OF THE VARIOUS ALTERNATIVE THERAPIES ACCORDING TO PRODUCT TYPE

PRODUCT TYPE	UNIT COST (€)/IU	MEAN ANNUAL COST/ ADULT PATIENTS	MEAN ANNUAL COST/ CHILDREN AND ADOLESCENTS
Plasma derivatives	0.45*	147 420	63 180
Second generation	0.69*	226 044	96 876
Third generation			
Advate	0.75	245 700	105 300
Refacto	0.69	226 044	96 876

\*mean unit cost for the category referred to

factors present higher annual costs than plasma derivatives. However, this difference may be justified by the multiple advantages associated with such therapies, in particular in terms of the increase in quality of life for hemophilia sufferers and the greater compliance of patients with the therapy (for these aspects, see Chapter 6).

Following upon this, mean annual costs were calculated per adult patient (30 IU/70 kg) and per child/adolescent (30 IU/30 kg) for the various therapeutic alternatives, aggregated according to product type (plasma derivatives, second-generation or third-generation product), keeping to the basis of a frequency of administration of three times per week (Table 8).

### Hospitalization costs

Because of its gravity and chronic nature, hemophilia is a costly disease (38-40). Hemophilic patients risk severe hemorrhages even following interventions that in themselves would be simple operations free of complications such as tooth extractions or uncomplicated surgery, and are exposed to arthromuscular problems due to repeated and spontaneous bleeding in the joints and muscles or to post-traumatic bleeding. Because of this, they require regular stays in hospital for orthopedic interventions, both minor and major, such as joint prostheses, especially of the knee and hip. During the period of hospitalization for the hemophiliac and for patients of coagulation diseases in general, patients have to practice substitution therapy, which consists in the administration of a concentrate of the deficient factor, in order to be able to undergo the surgical intervention and post-operative rehabilitation without risk of bleeding complications.

To provide an overview, the hospitalization rate has been calculated for hemophilic patients and this is compared to the number of discharges for the resident population. From the archive of hospital discharge forms (SDO), which may be accessed on the site of the Italian Health Ministry (41), updated to 2005, the number of hospital discharges was extracted whose main diagnoses and average reason for hospitalization are due to congenital factor-VIII disorders (ICD-9-CM: 286.0). When using the SDO archive, only the principal diagnosis can be factored and this could lead to an underestimate of the phenomenon under study. The population data used for the hospitalization denominator were extrapolated from the Health For All - Italia software available from the national statistical institute, ISTAT (42).

Table 9 shows the hospital discharge rate for males only, given that females are rarely affected by the disorder.

In Italy in 2005, the numbers of males discharged for congenital factor-VIII disorders were 220 in ordinary hospitalization regimes (ROs) and 1 384 in Day-Case (DH) visits. Considering RO stays, children aged between one and four years represented the largest proportion (35%), and this category, along with the age-group 5-14 years, was also the most represented in discharges from DH regime stays (approx. 24%).

The mean length of stay in RO regime for the 220 males was 5.89 days; elderly patients (65-74 years), on the other hand show a longer mean duration of 12.08 days.

If we compare the absolute number of discharges with the male population resident in Italy, the same pattern emerges, especially in the case of DH regimes. In fact, children aged

TABLE 9

NUMBER OF (MALE) DISCHARGES FOR CONGENITAL DISORDERS OF FACTOR VIII IN RO AND DH REGIMES, RESIDENT MALE POPULATION AND HOSPITAL DISCHARGE RATES (PER 100 000) IN RO AND DH REGIMES - 2005

AGE GROUP	RO DISCHARGES	MEAN STAY	DH DISCHARGES	RESIDENT MALE POPULATION	RATE OF RO HOSPITAL DISCHARGES	RATE OF DH HOSPITAL DISCHARGES
< 1 year	24	7.80	21	284 472	8.44	7.38
1-4 years	78	4.43	339	1 117 901	6.98	30.32
5-14 years	25	4.41	343	2 839 647	0.88	12.08
15-24 years	12	5.67	186	3 124 386	0.38	5.95
25-44 years	28	6.04	305	9 069 743	0.31	3.36
45-64 years	29	5.42	151	7 223 485	0.40	2.09
65-74 years	13	12.08	27	2 792 032	0.47	0.97
≥ 75 years	11	9.28	12	1 925 138	0.57	0.62
Total	220	5.89	1 384	28 376 804	0.78	4.88

1-4 years had the highest rate of discharge from DH regimes for congenital disorders of factor VIII in DH regime (30.32 per 100 000), while the highest proportion observed in RO regime is of neonates (8.44 per 100 000). Taking the male population as a whole, discharge rates were 0.78 and 4.88 (per 100 000) in RO and in DH regimes respectively. No clear pattern emerges across age groups.

Direct hospitalization costs were calculated using the DRG tariff scales given in Ministerial Decree of September 12 2006 as cost proxies (31). Following the study by Gringeri et al. (17), two DRG codes were taken into consideration: Code 397 - Coagulation Disorders - and 209 -Interventions on major joints and replants in lower limbs. Tariffs are given in Euro 2010 (Table 10). As it was not possible to obtain the exact number of Hemophilia A patients for each DRG, in order to calculate the direct costs attributable to hospitalizations, the number of Hemophilia A patients for the two DRG codes under consideration was estimated and this value was then multiplied by the DRG tariffs (Table 11). The number of hospital discharges of Hemophilia A patients treated under DRG 397 was estimated by applying the percentage of 27% to the number of hospitalizations (5 252 males) for this DRG, as extrapolated from the SDO discharge archive (41). The 27% figure was obtained from the proportion of male patients with mild-severe Hemophilia A among all coagulation disease patients in Italy (7 899) according to the ISTISAN Report (43).

The number of Hemophilia A sufferers attributable to DRG 209 was calculated by using

Gringeri et al.'s (17) findings that a Hemophilia A patient who has developed inhibitors undergoes a mean of 0.09 orthopedic surgical interventions per year and that hemophiliacs with inhibitors have twice the probability of being hospitalized for complications due to hemorrhaging compared to those without inhibitors (44). Multiplying the number of male Hemophilia A patients present in Italy (3 307), according to the ISTITAN 10/31 Report (see Chapter 1), by the corrective factor of 0.045, obtained from the above considerations, we obtain an estimate for the number of sufferers from Hemophilia A, who have been discharged under DRG 209. The overall costs in Italy attributable to Hemophilia A thus total approximately €8 million per year, with a minimum percentage attributable to interventions for joint replacements. The mean annual cost per patient comes out at €2 461.91.

It should here be stressed that, due to the paucity of available data, an assessment of the amount of resources attributable to hospitalizations, arrived at by such an analysis, has to be treated only as an estimate of the actual deployment of resources for sufferers from Hemophilia A.

#### Other costs

For a comprehensive overview of direct healthcare costs, the reader is referred to the study conducted by Gringeri et al. (17), in which other kinds of costs are quantified. For an estimate of the total annual costs for other



TABLE 10

DRGs ATTRIBUTABLE TO HEMOPHILIA A IN RO REGIME (EURO 2010)				
DRG	NAME	DIRECT COSTS/PATIENT IN RO (€)	THRESHOLD VALUE*	INCREASE PER DAY
397	Coagulation disorders	4 814.60	20	161.58
209	Interventions on major joints and replants in lower limbs	8 821.63	26	100.00

\*The threshold value is the number of hospitalization days above which an admission comes to be considered anomalous and for which an additional payment is applicable.

Modified from the Italian Ministry of Health (31)

TABLE 11

ANNUAL HOSPITAL-RELATED COSTS (EURO 2010)			
DRG (VERSION 19)	ESTIMATE OF NUMBERS ADMITTED IN RO	DRG RO TARIFF (€)	ANNUAL ESTIMATED COST (€)
397	1 418	4 814.60	6 827 102.80
209	149	8 821.63	1 314 422.87
Total			8 141 525.67

categories, the number of patient visits was multiplied by the unit cost of the resource deployed, as extrapolated from the above-cited study. This value was then multiplied by the number of male Hemophilia A patients (3 307) in Italy, according to the ISTISAN Report (43) (Table 12). The mean annual cost per patient comes out at €229.56.

### Mean annual per-patient costs

Table 13 shows estimated total mean annual costs for the management of hemophilic patients. As can be seen from the Table, the cost of drugs constitutes the principal cost driver (98-99% of the total). This is followed by costs associated with hospitalizations, by other costs, and by costs of diagnosis.

### Costs for patients with inhibitors

Both in this chapter and in the preceding ones, mention has been repeatedly made of the complex nature of managing what today represents one of the major issues

facing hemophilia treatment: the appearance of inhibitors to the factor being infused. This issue is today one of central interest for the scientific community. Apart from the impact it has on the already fragile quality of life of hemophilic patients, it adds a further and considerable complication to clinical management, above all in terms of the dramatic increase in costs it entails. This section will therefore assess the direct mean annual costs for patients who develop inhibitors.

According to the ISTISAN Report (43), the total number of such patients is 352. Under the headings of Diagnosis and Other Costs, mean annual per-patient costs are €21.72 and €229.56, respectively. The assumptions described above apply to the calculation of these cost items. With regard to hospitalization, costs were estimated with reference to the admission percentages of 37% for inhibitor-affected patients for DRG 397 and of 20% for DRG 209, as reported in the Gringeri study (17).

As can be seen from Table 14, the total annual cost for Hemophilia A patients with inhibitors is approximately €1.2 million. The mean annual cost per patient comes out at €3 545.18. Mean annual costs for pharmaceutical

TABLE 12

OTHER COSTS (EURO 2010)			
SERVICE	NUMBER OF VISITS (PATIENT /ANNUM)	UNIT COSTS (€)	ESTIMATED TOTAL ANNUAL COSTS (€)
Dental surgery	n.a.	16.1	-
Visits to specialized hemophilia centers	6.7	20.8	460 306.1
Physiotherapy visits	10.4	8.7	298 855.3
Total			759 161.4

n.a. = data not available  
Modified from Gringeri (17)

TABLE 13

MEAN ANNUAL PER-PATIENT COSTS, ADULTS				
COST ITEMS	PLASMA DERIVATIVES	SECOND GENERATION	THIRD GENERATION ADVATE	THIRD GENERATION REFACTO
Diagnosis	21.72	21.72	21.72	21.72
Drug	147 420	226 044	245 700	226 044
Hospitalization costs	2 461.91	2 461.91	2 461.91	2 461.91
Other costs	229.56	229.56	229.56	229.56
Total annual per-patient costs	150 133.19	228 757.19	248 413.19	228 757.19

TABLE 14

ANNUAL HOSPITAL-RELATED COSTS (EURO 2010) FOR PATIENTS WITH INHIBITORS			
DRG (VERSION 19)	ESTIMATE OF NUMBERS ADMITTED	DRG RO TARIFF (€)	ANNUAL ESTIMATED COST (€)
397	130.2	4 814.60	626 860.92
209	70.4	8 821.63	621 042.75
Total			1 247 903.67

treatment (Table 15) were calculated using the figures in the study by Gringeri et al. (17). With this category of patient in particular, various product types are administered according to the therapeutic approach used: bypassing agents (coagulation factor VIIa from recombinant DNA - rFVIIa - and activated prothrombin complex) and/or factor VIII - plasma-derived or recombinant (for a more comprehensive overview of management of

patients with inhibitors, see Chapter 2).

This analysis yields a mean annual cost per patient with inhibitor of €217 987.7, of which 98.3% is attributable to pharmaceutical treatment. For patients with inhibitors in particular, the infusion of FVIIa represents the main cost driver (Table 15). The study by Gringeri et al. also shows that the mean cost per surgical intervention using rFVIIa equals €256 000. Here it must be stressed

TABLE 15

## MEAN ANNUAL DRUG-TREATMENT COSTS PER PATIENT WITH INHIBITORS (EURO 2010)

DRUGS USED	COSTS PATIENT/ MONTH	MEAN COSTS PATIENT/ ANNUM
rFVIIa	8 551.34	102 616.08
Recombinant factor VIII	3 196.42	38 357.04
Plasma-derived factor VIII	3 098.64	37 183.68
Activated prothrombin complex concentrate	3 002.87	36 034.44
Total pharmaceutical costs	17 849.27	214 191.24

Modified from Gringeri (17)

that this figure is an under-estimate, given that patients who develop inhibitors may be subjected to a special therapeutic regime of prophylaxis with FVIII, which has the main objective of eradicating the inhibitor itself (induction of immune tolerance - ITI). This approach of inducing immune tolerance inevitably entails a sizeable increase in the amount of resources involved. As reported in the study by Negrini et al (2009), the induction of immune tolerance calls for a very high initial investment. Auerswald et al. (45) estimated that ITI entails an average cost per patient with inhibitor ranging from €421 740 for a low-responder child to €1 150 200 for a high-responder child, while for an adult the cost ranges between €575 100 and €5 751 000.

Confirming this, a study by Knight et al. (46) reports mean annual ITI costs per (high responder) patient according to the various protocols of: Bonn (€4 862 326), Malmö (€2 983 563) and Low-Dose (€3 500 327).

In view of the great management costs inherent in the adoption of ITI regimes, increasing interest is paid today to the identification of therapeutic strategies and business practices that may, in to some extent, limit their economic impact.

As has been emphasized previously with regard to the immunogenicity of products for treating hemophilia (see Chapter 2), the EMA has laid down that the assessment of the risk of developing inhibitors in connection with a given concentrate must be conducted using patients who have previously been treated (PTPs) and not using patients new to such treatments (PUPs).

The same European agency also

established that post-marketing surveillance studies play a fundamental role in assessing the safety of pharmacological therapies: as they involve large non-selected populations that have been treated according to routine clinical practice; they produce information about the drug that reflects actual clinical context (48). This observation becomes even more relevant in the case of rare pathologies such as hemophilia, where data derived from clinical trials are partial and often relate to small samples. Data deriving from post-marketing surveillance studies therefore represents a sound basis from which to quantify the costs of hemophilia therapy with and without inhibitors. In general, costs relating to the onset of inhibitors can vary greatly according to whether the inhibitors disappear spontaneously, whether immune tolerance therapy (ITI) is enacted, whether this is effective or not, and whether the patient requires chronic use of bypassing agents. For this reason, a need exists for an estimate of the impact of the onset of inhibitors on the overall cost of substitution therapy for Hemophilia A: a calculation of the variation in total cost as a function of product used and of the incidence and severity of the inhibitor.

In view of the high costs of treating patients in whom inhibitors develop, there is an urgent need for a comprehensive assessment of the financial implications for the National Healthcare System (the Italian SSN) in its treatment of hemophiliacs. This is indeed the aim of a study currently under way, which involves the collaboration of Baxter with the College of S. Anna in Pisa.

## CONCLUSION

The management of patients with hemophilia has improved over the years thanks to the introduction of effective and increasingly safer treatments. This has been associated with a considerable consumption of both economic and human resources, given the complexity of the disorder, particularly when hemophiliacs develop inhibitory antibodies or articular complications.

From the analysis, it can be seen that infusion of factor VIII constitutes the principal cost driver (97-98% of the total). As confirmed by the available literature, this is followed by costs associated with hospitalizations, by other costs, and by diagnostics.

From a comparison of estimates of the costs of the various therapeutic alternatives, it can be seen that drugs containing recombinant factors represent higher annual costs than plasma derivatives.

Hemophilic patients risk severe hemorrhages even following interventions that in themselves would be simple operations free of complications. Having arthromuscular problems due to repeated bleeding in the joints and muscles, they require regular stays in hospital. Hospitalization costs amount to €12 million per year, with a minimum percentage attributable to interventions for joint replacements (DRG 209).

Mean annual per-patient costs for

Hemophilia A in Italy range from €150 133.19 to €248 413.19 according to type of drug treatment (plasma derivatives, second and third generation) which the adult patient undergoes.

The sub-group of patients who develop inhibitors was also considered, as their management involves special treatments and safeguards, particularly with regard to their pharmacological treatment. The mean annual cost per patient with inhibitor was estimated to be €217 987.7, of which 98.3% is attributable to pharmaceutical treatment. It must be stressed that this figure is an underestimate as the substantial costs involved in actuating a therapeutic regime of inducing immune tolerance (ITI), aimed at eradicating inhibitor present in the circulation has to be considered. However, in view of the great management costs inherent in the adoption of ITI regimes, increasing interest is being paid today to the identification of therapeutic strategies and business practices that may, to some extent, limit their economic impact. To this end, Baxter has recently proposed an innovative model of public-private partnership to benefit patients through facilitated access to the ITI therapeutic approach.

Finally, it should be borne in mind that increasing life-expectancy among hemophiliacs will bring with it increases in the costs of managing this disorder as it is aggravated by the typical diseases of ageing.

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## 4. Biotechnology, efficacy and safety of Advate

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### INTRODUCTION

Chapter 2 described the marked evolution of Hemophilia A treatment over the past 30 years.

Starting from the 1970s, the availability of new and efficacious clinical viral treatments has allowed hemophiliacs to attain a life expectancy in line with that of the general population. This positive trend was countered in the 1980s by the tragedy of viral contamination of drugs and the consequent infection of patients with HIV, HCV and HBV viruses.

These dramatic events caused research to focus not only on efficacy of treatment but also on safety from contamination by blood-borne pathogens. Over time, thanks to the availability of ever safer compositions in terms of viral safety, the focus moved towards their potential immunogenicity, an aspect now held to be a challenge due to the great clinical complexity of handling patients who develop inhibitors.

A comprehensive review of anti-hemophiliac treatment cannot therefore exclude any of these aspects, all of which are aimed at guaranteeing extremely safe and efficacious treatment options to patients.

Advate, a full-length-molecule recombinant human FVIII of the latest generation, offers patients a complete treatment option. Advate is the first factor VIII (FVIII) full-length-molecule recombinant to be produced without added plasma or albumin. The absence of added human and/or animal components in all phases of production effectively cancels the risk of transmission of blood-borne pathogens (1).

Advate thus represents the summit of 20 years of Baxter's research, in which the aim has been to make ever safer products for hemophiliacs. The success of this research program has been recognized by the CPMP (Committee for Proprietary Medicinal Products) who has ratified the following:

*"In the effort to increase product safety,*

*Advate has been developed by introducing alterations to its fermentation, to its purification process and to its final formulation, which have nullified the need for recourse to components and excipients of human or animal origin, for all its production phases" (1).*

This chapter will review the product's main features, looking at the efficacy, safety, immunogenicity and ease of use of Advate.

### CLINICAL EFFICACY OF ADVATE

The clinical efficacy of Advate has been demonstrated in four pilot clinical regulatory trials and in several post-authorization studies. A short summary of the results follows.

Advate's hemostatic efficacy was tested in the pilot regulatory trial based on a sample population of 111 previously treated patients (PTPs;  $\geq 150$  exposure days). The results of this pilot study, illustrated in Figure 1, show that in 93% of participants hemorrhage was resolved with 1-2 infusions (2). In the same study, 88% of patients treated with Advate showed improvement in the signs of hemorrhage and/or relief from pain encountered during these bleeding episodes.

### TARANTINO 2004

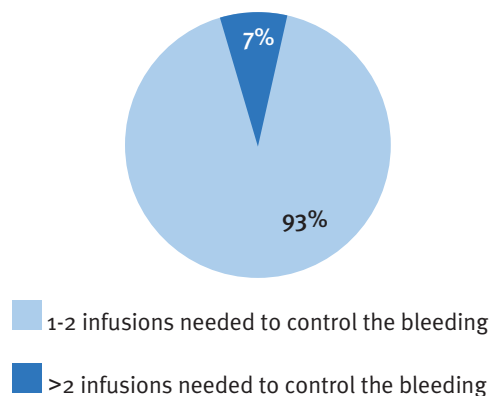
Tarantino et al. published the results of the pilot, regulatory trial study for Advate conducted on previously treated adolescents and adults suffering from moderately severe to severe Hemophilia A (factor VIII levels  $\leq 2\%$  of normal) (2).

The study, which involved 108 patients, was composed of three parts:

- The first part was a randomized double-blind crossover, pharmacokinetic comparison study between Recombinate

FIGURE 1

PERCENTAGE OF HEMORRHAGES RESOLVED WITH 1-2 INFUSIONS USING ADVATE WITH PTPS  
(NUMBER OF HEMORRHAGES = 510, TARANTINO (2))



and Advate, produced in a pilot-scale batch in one of Baxter's plants (Orth, Austria).

- The second part was in an open label, non-controlled study, in order to evaluate the efficacy, safety and immunogenicity of prophylaxis with Advate, produced in a pilot-scale batch in Baxter's plant at Orth.
- The third part was completely analogous to the first, but used an industrial-scale batch of Advate produced in the Neuchatel (Switzerland) plant.
- During this study, participants received a total of 12 597 infusions of Advate.

Efficacy trial results:

- Of the 510 bleeding episodes, 93% of those treated with Advate were managed with 1-2 infusions of the product, while 81% were resolved with a single infusion.
- 86% of patients treated with Advate showed improvement in the signs of hemorrhage and/or pain relief during the bleeding episodes (assessed as excellent or good).
- 30% of subjects on prophylaxis with Advate were free of bleeding episodes.
- It was demonstrated that Advate is bioequivalent to Recombinate. The overall incidence of hemorrhage during the prophylactic regime was 6.3 episodes per patient per year.
- Patients who kept to the prescribed doses and frequencies of prophylaxis had an annual hemorrhage frequency of 4.4%, a reduction of 76% compared to patients who did not comply with the prophylaxis.

Safety trial results:

- 19 non-severe adverse events (0.15% of infusions), in 7 participants, were considered to be correlated to the use of Advate.
- Throughout the whole study, only one transitory inhibitor, clinically silent and of low titer, was observed with Advate.

The authors therefore concluded that Advate is efficacious and safe without any increase in immunogenicity.

## BLANCHETTE 2008

The pharmacokinetics of Advate in children was reported by Blanchette et al. (2008). This was the first prospective study aimed at evaluating rFVIII pharmacokinetics in a relatively broad cohort of children aged less than 6 years (3).

Study design:

- Multi-centered open label prospective cohort study.
- 53 Previously treated patients (PTPs) less than 6 years of age.
- 7 980 Advate infusions administered overall.

Efficacy trial results:

- Annual median number of intra-joint bleeding episodes equal to 0 for patients in prophylaxis.



- 90.1% of bleeding episodes were managed with one or two infusions of Advate (Figure 2).
- Hemostatic efficacy was found to be excellent or good in 94% of bleeding episodes taken into consideration.
- Patients undergoing prophylaxis had 84% fewer hemorrhages than patients treated on an on-demand basis (this difference, however, is not statistically significant due to the low number of patients being treated on-demand).
- For children under 6 years of age, FVIII appears to have a shorter half-life ( $t_{1/2}$ ) and a lower *in vivo* recovery (IVR) compared to older patients. Both parameters increased with age ( $t_{1/2}$ ) and body mass index (adjusted IVR) (3).

#### Safety trial results

- No inhibitors and no severe adverse event were found in this study after 7 980 Advate infusions.
- No sign of increased immunogenicity among PTPs aged less than 6 years, when treated with Advate.

The authors concluded that Advate is an effective treatment, safe and non-immunogenic for previously treated children affected by Hemophilia A.

Baxter has continued studying the safety and efficacy of Advate in previously untreated patients (PUPs) aged less than 6 years (Advate PUP study currently in publication). This study aimed to enlist 50 PUPs aged less than 6 years with base-line levels of factor VIII of  $\leq 2\%$ .

## NEGRIER 2008

Negrier et al. published the results of a clinical study designed to analyze the efficacy and safety of Advate administered during surgical operations (4).

#### Study design:

- 59 PTPs aged  $\geq 5$  years and affected by moderately severe to severe Hemophilia A (factor VIII levels  $\leq 2\%$  of normal). Patients with a noticeable base-line inhibitor or with inhibitor history were excluded from the study.
- Administration of Advate in bolus or by continuous infusion in order to guarantee

hemostatic cover during surgery or dental procedures.

- 58 subjects underwent 65 procedures (one subject decided not to go ahead with the planned operation).
- 18 procedures were carried out using continuous infusion.

#### Results of the study:

- Hematic loss was found to be lower than expected within the expected range, in 95% of procedures in which Advate was used.
- Advate's hemostatic efficacy during surgery was considered excellent or good in 100% (61 out of 61) of the procedures taken into account.
- Advate's post-operative hemostatic efficacy was considered excellent or good in 100% (63 out of 63) of the procedures taken into account.
- No severe adverse event, including inhibitors, was considered to be correlated to Advate. No patient withdrew from the study because of an adverse event.

The authors of the study concluded that Advate is an effective and safe hemostatic agent, administered both in bolus and by continuous infusion to patients affected by Hemophilia A and undergoing surgery.

## Grouped data on clinical efficacy

The Global Study Program on Advate comprises 4 already completed PTP studies and a study on PUPs that has been completed but is not yet published (Table 1).

Results of the studies within the Advate Global Development Program, completed by 2009, have been grouped by Shapiro et al (2009) (5). Overall, the Global Clinical Program included 2 100 hemorrhage episodes treated in 234 participants, 209 of whom were subjected to prophylaxis.

#### The main results of the grouped data are:

- 90% of bleeding episodes were managed with one or two infusions of Advate (Figure 2).
- Advate's efficacy was considered to be excellent or good in 82-88% of joint hemorrhages.
- Advate's efficacy was considered to be excellent or good in 92-93% of non-joint hemorrhages.

FIGURE 2

PERCENTAGE OF HEMORRHAGES RESOLVED AFTER 1-2 INFUSIONS IN CHILDREN AGED < 6 YEARS  
(NUMBER OF HEMORRHAGES = 354, BLANCHETTE (3))

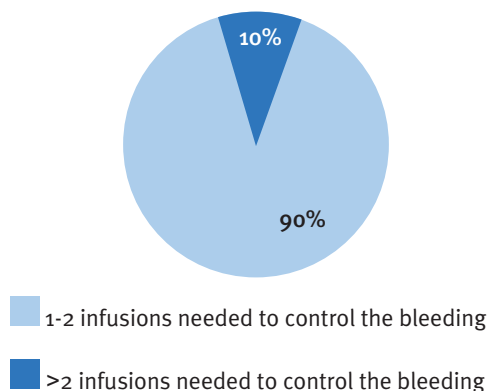


TABLE 1

GLOBAL PLAN OF ADVATE STUDY

Phase III pilot (Tarantino, 2004) (2)	Assessment of the pharmacokinetics (double-blind, randomized, crossover), safety, immunogenicity and hemostatic efficacy (open label) in a European and US cohort of PTPs ≥ 10 years of age	Completed
Continuation (Gruppo 2006, published as an abstract)	Assessment of pharmacokinetics, safety, immunogenicity and hemostatic efficacy (open label) in PTPs who continued the pilot study	Completed
Surgery (Negrier 2008) (4)	Assessment of the pharmacokinetics, immunogenicity and hemostatic efficacy (open label) for peri-operative management in a European and North American cohort of PTPs aged ≥ 5 years	Completed
Pediatric PTPs (Blanchette 2008) (3)	Assessment of pharmacokinetics, safety, immunogenicity and hemostatic efficacy, including peri-operative management (open label), in a European and North American cohort of PTPs aged ≤ 6 years	Completed
PUP study (in publication)	Assessment of pharmacokinetics, safety, immunogenicity and hemostatic efficacy, (open label) in a global cohort of PUPs aged ≤ 6 years	Completed

- Subjects who underwent prophylaxis suffered bleeding episodes less frequently than those treated on demand: the annual median number of bleedings was 3 (95% CIs: 1-3) and 3.9 (95% CIs: 3-4) respectively for patients undergoing prophylaxis as defined by the protocol or by the investigator, compared to 6.3 (95% CIs: 3-12; n=26) for patients undergoing treatment on demand.
- For patients undergoing any kind of prophylaxis regime, compliance with treatment was found to be strongly correlated

- to a lower frequency of bleeding episodes.
- In the Global Clinical Development Program carried out on 198 PTPs with ≥ 10 exposure days and/or 6 months' observation, on PTPs affected by severe to moderately severe Hemophilia A (FVIII levels ≤ 2% of normal), the cumulative incidence of development of inhibitor to factor VIII was 0.51% (95% CIs, 0.03%-2.91%) (5).

The Global Clinical Development Program data suggest that Advate is effective in

treating bleeding episodes in patients suffering from severe to moderately severe Hemophilia A, with a hemostatic efficacy equivalent to that reported for other full-length-molecule FVIII concentrates. These results confirm the efficacy of Advate in prophylaxis in reducing the incidence of bleeding episodes.

These findings also demonstrate Advate's low immunogenicity. During the Global Clinical Development Program, in one patient only there was only one case of a low titer of inhibitor, which was recurrent, non-persistent and clinically non-significant (5).

### CLINICAL EFFICACY OF ADVATE IN ROUTINE APPLICATION

The PASS (Post-Authorization Safety Surveillance) prospective study non-intervention program on Advate's safety was launched in 2004 to record Advate's safety and efficacy in routine daily clinical practice (6).

Study design of Advate PASS (6):

- Observational, prospective, open label and non-controlled study
- 521 patients treated with at least one Advate infusion (82% enrolled in Europe, 18% in the USA) of whom 457 (88%) were PTPs who had been treated with other recombinant or plasma-derived drugs.
- 224 (43%) patients treated on demand, 297 (57%) in prophylaxis.
- 10.9% of patients with history of inhibitor to FVIII

Efficacy results (6):

- Advate's efficacy was assessed as excellent/good in 95% and 92% of patients treated respectively on demand and in prophylaxis.
- In all 16 surgical procedures carried out in the USA arm, Advate's efficacy was always deemed excellent/good.

Safety results (6):

- A low titer new-onset inhibitor was recorded in 348 PTPs with factor VIII  $\leq$  2% (severe/moderately severe hemophilia) without a history of inhibitors (incidence 0.29% [95% CIs, 0.01%-1.59%]).
- There was no evidence of an increased risk of inhibitors after the change from a

plasma-derived or recombinant factor VIII to Advate.

The PASS Advate study confirms in actual routine clinical practice on a vast study population, what had been demonstrated in the clinical development program of Advate, i.e. that Advate is indeed effective and has low immunogenicity.

### OCTOCOG ALFA: ADVATE'S ACTIVE INGREDIENT, AND THE IMPORTANCE OF THE INTACT MOLECULAR STRUCTURE

In nature, the molecule of the human FVIII protein is synthesized as a monomer made up of repeated domains A1, A2 + A3, C1 + C2 and by a single Domain B. Each of the three domains of the FVIII protein has its own specific function, whether more or less direct, within the FVIII life cycle.

When it is formed, FVIII is molecule made up of a heterodimeric complex composed of heavy and light chains, associated by means of a cation. This dimer is linked in a non-covalent way to the Von Willebrand Factor (VWF), which acts as a stabilizer.

During induced secretion and activation of thrombin (FIIa), as well as during the following inactivation mediated by activated protein C (APC), FVIII is subject to several proteolytic scissions during which Domain B is removed and the light and heavy chains are broken down further.

During the activation phase of FVIII, its domain B is removed from the heavy chain of FVIII itself. Following activation, it is assumed that domain B no longer plays a role in the life cycle of FVIII. Nevertheless, even if not indispensable for FVII's coagulation activity, domain B has other functions that influence the life cycle of FVIII itself (Table 2).

Advate's active principle is octocog alfa, a glycoprotein produced by recombinant DNA technology. Octocog alfa is made up of a sequence of 2 332 amino acids with a molecular weight of approximately 280kD. After the glycosylation process, this molecular weight increases to over 300kD. The sequence of amino acids of the Advate molecule is completely similar to that of human FVIII and the post-translation alterations to which the molecule is itself subjected are analogous to those that take place in the plasma-derived molecule. The single-strand protein is processed rapidly

TABLE 2

## THE ROLE OF B DOMAIN IN THE FVIII LIFE CYCLE

Synthesis	Mediates the recovery of poorly folded molecules during the cell culture production phase, guaranteeing their absence from the end product (11, 12)
Secretion	Improves the transportation from the endoplasmic reticulum to the Golgi bodies (13, 14)
Platelet bond	Improves bonding of activated platelets (15, 16)
Activation	Achieves accelerated thrombin proteolysis (17)
Inactivation	Slows down induced proteolysis of activated Factor Xa C protein (18)

in the culture medium in order to obtain a heterodimer made up of a single chain with a molecular weight of 80 kD, derived from the terminal-C unit, as well as of a family of heavy chains whose molecular weights range between 90 kD and 210 kD. Among these is the N-terminal sequence weighing 90 kD, and domain B. Even if it is not necessary to the activity of FVIII's co-factor, domain B contains 19 of the 25 potential N-linked glycosylation sites. Furthermore, domain B also contains almost all of the 10-12 O-linked glycosylation sites of the FIII protein (1).

On the assumption that domain B plays no direct pro-coagulation role, part of the research in this field has focused on synthesizing and subsequently producing drugs known as B-domain-deleted (BDD) FVIII (Moroctocog alfa - ReFacto AF), which are without domain B (Table 3).

In view of B domain's functional roles as described above, which have an influence on the life cycle of FVIII, it is postulated that its elimination could have repercussions on the clinical effects of BDD drugs. Indeed, there is evidence *in vitro* of a greater efficacy of full-length-molecule factor VIII compared to FVIII without domain B (BDD-FVIII) (16). Also, through its interaction with proteic molecular chaperones during intracellular processing, domain B could prevent the creation and release of abnormal FVIII molecules (9) which seem to be linked to an increased risk of induction in the development of inhibitors (17).

Studies conducted on hemophilic patients appear to confirm *in-vitro* observations of a possible difference in clinical efficacy between full-length-molecule factor VIII (FL-FVIII), such as Advate, and BDD-FVIII, such as ReFacto AF (16, 18).

A meta-analysis of 13 observational studies

on prophylaxis treatments, which considered data on the frequency of intercurrent bleeding during prophylaxis with FL-FVIII and with BDD-FVIII, has revealed significant differences in the hemostatic efficacy of the two product types (Figure 3) (16).

The grouped datum on the incidence of bleeding in patients treated with FL-FVIII was of 6.6 hemorrhages per patient per year (95% CIs, 4.7-8.5 hemorrhages per patient per year). The corresponding incidence in patients treated with BDD-FVIII was of 16.8 hemorrhages per patient per year (95% CIs, 9.5-24.2 hemorrhages per patient per year), more than 2.5 times higher than the finding for FL-FVIII ( $P < 0.0005$ ).

Furthermore, in the same study, the weekly cumulative dosage of prophylaxis with BDD-FVIII ( $81.3 \pm 13.8 \text{ UI kg}^{-1} \text{ week}^{-1}$ ) was 36% higher than the prophylaxis dosage with FL-FVIII ( $60.0 \pm 5.9 \text{ IU kg}^{-1} \text{ week}^{-1}$ ) (Figure 4). Although this difference is not statistically significant, a doubt lingers regarding its potential relevant impact in actual clinical practice. In fact, the differences in costs that may be associated with larger doses of BDD-FVIII could be relevant in clinical and pharmaco-economic terms.

Further evidence of possible differences in rates of consumption has recently been provided by a retrospective study conducted by Epstein et al. (2009), in which it was observed that patients treated prophylactically with BDD-FVIII consumed 27% more product per year ( $p=0.04$ ) compared to patients treated with FL-FVIII. The authors accounted for the increase in BDD-FVIII consumption with an increased requirement for the factor, even though the prescribed dosages were similar for both products used (19).

In an observational study conducted on ReFacto (20), the authors observed that the

TABLE 3

FVIII PRODUCT GENERATIONS AND DESCRIPTION OF B DOMAIN			
GENE EXPRESSED	FIRST GENERATION	SECOND GENERATION	THIRD GENERATION
rFVIII BDD	N.A.	ReFacto	ReFacto AF
rFVIII FL	Recombinate	Kogenate FS Helixate FS	Advate

N.A.: not available

FIGURE 3

TOTAL NUMBER OF HEMORRHAGES PER PATIENT PER YEAR, BASED ON A COMPARISON BETWEEN FL-FVIII AND BDD-FVIII (19)

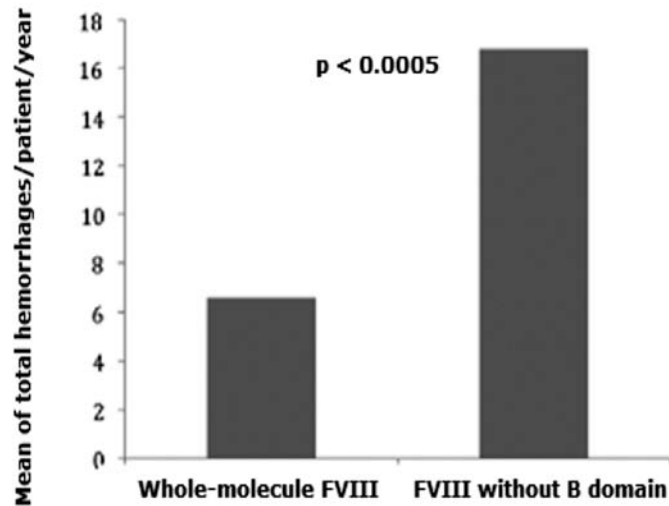
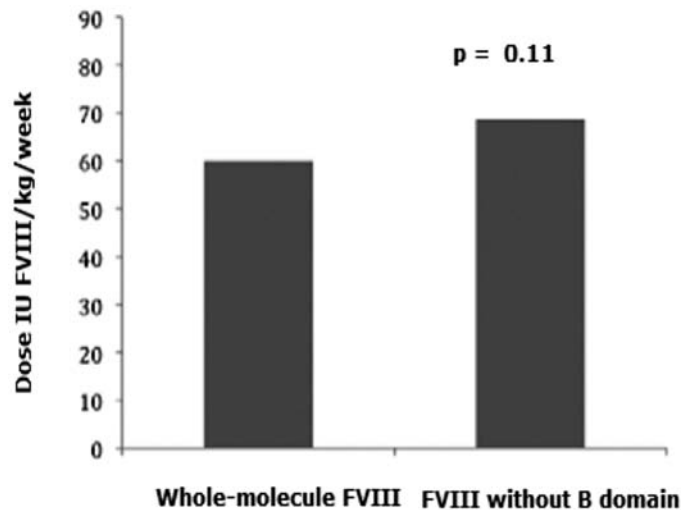


FIGURE 4

GROUPED DATA OF MEAN DOSAGES OF FL-FVIII AND BDD-FVIII (19)



“therapeutic effect was less than expected”. By the end of the study, 96/217 patients (44.2%) had interrupted treatment, prematurely; 40% of these did so due to a lack of therapeutic response.

In light of this evidence – which suggests a lack of efficacy of BDD-FVIII (20) – and taking into consideration the results of the meta-analysis by Gruppo et al. (2003) (16), which show higher frequencies of hemorrhages in patients treated with BDD-FVIII compared to FL-FVIII, the Summary of Product Characteristics (SPC) for ReFacto was updated to include the warning that some signs of a lack of efficacy had been reported during clinical trials and during post-marketing surveillance, especially for patients in prophylaxis.

This warning, introduced in ReFacto’s SPC, alone among hemophilia drugs, was also included in the SPC of ReFacto AF, the third generation version of this product.

The reasons for this episodic lack in hemostatic response of BDD products could be sought in the half-life of the product itself. A recent crossover study, reported in the EPAR (European Public Assessment Report) for ReFacto AF, has indeed shown, on the same group of patients, that the mean half-life of Advate is 2.0 hours longer than that of rFVIII-BDD (21, 22). Collins et al. have shown that for patients in prophylaxis, it is the drug’s half-life, together with the patient’s pharmacokinetic response, that determines the maintenance of FVIII at a >1% trough level. This is the threshold value for effective prevention of bleeding and its sequelae (23, 24).

Doubts still remain whether the elimination of the B domain might also be associated with a higher risk of developing inhibitors (25); evidence exists (the study CANAL-Concerted Action on Neutralizing Antibodies in severe Hemophilia A), to suggest that patients treated with BDD-FVIII might tend to have a higher risk of developing inhibitors (26-28).

## ADVATE. BIOTECHNOLOGY AND SAFETY AGAINST PATHOGENS

Advate is the only concentrate of full-length-molecule recombinant FVIII that does not use human or animal plasma components in the cell culture medium. This is why Advate has removed any risk of transmission of any kind of blood-borne pathogens, be they

known, unknown or emerging (EMA, 2005) (1). The exclusion of human and animal plasma proteins also removes the risk of contamination by prions, such as those that cause the variation of the Creutzfeldt-Jakob (vCJD) disease (29).

The most important difference between plasma-derived and recombinant products is the production process and the related differences in the risks involved of pathogen transmission. As noted above, the use in the past of plasma-derived products led to pathogen transmission, which in some countries caused HIV contagion in more than 50% of persons affected by hemophilia. However, the adoption of ever more precise methods of viral removal and donor selection has reduced enormously the risk of transmission of HIV, HCV and HBV linked to plasma-derived FVIII.

Uncertainty, however, remains over whether these methods of screening and control of known pathogens, which have been introduced over the past 20 years, are effective in protecting against potential new pathogenic agents.

For this reason, regarding plasma-derived products, the US Medical and Scientific Advisory Council (MASAC) states (30):

*The possibility remains of the viral transmission of HIV-1, HIV-2 or hepatitis B or C with the use of the virus-inactivated plasma-derived products currently on the market. Plasma-derived factor VIII has also transmitted viruses free of a lipid envelope, such as the human B19 parvovirus and hepatitis A virus; therefore further stages such as viral filtering have been added in order to reduce these risks”.*

### MASAC Recommendation #182

Based on the above considerations, both international organizations and the clinical guidelines drawn up by scientific associations recommend recombinant products as the treatment of choice for people affected by Hemophilia A (30, 31).

In its Recommendation No. 182 (30), MASAC provides a detailed explanation of Advate’s safety features. In that same document, mention is made of the importance of protection from possible emergent infections.

Apart from safety, the introduction of recombinant products has led to improvements in the availability of drug supplies, since production lines based on cell cultures eliminate dependency on plasma donations.

According to MASAC in the USA, recombinant factor VIII products are classified

as first-, second- or third-generation products according to incremental improvements (Table 4) (32). First-generation products, however, are no longer marketed in Italy.

Some specific features of Advate prevent the transmission of known and of possible future emergent pathogens (1). These include (see Table 5):

1. The use of a cell line from the Chinese Hamster Ovary - (CHO)
2. The composition of the cell culture medium
3. A protein-free purification process
4. Stabilizers in the end product

The genetically engineered cell, CHO, which produces Advate, uses a protein-free culture medium. All the amino acids employed as cell-culture medium are of non-animal origin (1). As the cell line derives from the hamster, the CHO cells are resistant to human viruses that are unable to cross the human-species/animal-species barrier.

The CHO cell line, from which Advate's cell line derives, was isolated many years before currently well-established blood-borne pathogens arose (33). HIV, HCV, the variant of the Creutzfeldt-Jakob disease (vCJD), the West Nile virus, SARS and simian smallpox emerged as possible threats to the community in the period after the designing of the CHO cell-line. For instance, the first confirmed cases of West Nile Virus transmitted by blood components were recorded in the USA in 2002. During this period, the Master Cell Bank used for Advate's cell line was kept in an isolated laboratory environment, with no possibility of exposure to human or hamster viruses.

For the production of Advate, cell banks of monoclonal antibodies were adapted for production using media that are free of serum

or plasma. Similarly, Advate is purified from the cell-culture medium by chromatography using monoclonal antibodies derived from cell banks that were themselves adapted for production using media free of plasma components of human or animal origin (34).

The safety of Advate was further improved by the introduction to the production process of a viral inactivation stage using solvent-detergent (1).

Advate represents the gold standard in terms of safety against pathogens because:

- No additives of human or animal origin are used in any of its production stages (1).

The absence of additives of human or animal origin eliminates the risk of transmission of pathogens, either known or arising in the future (1).

- The exclusion of human and animal origin components also eliminates the risk of contamination by prions, such as those that cause the variant of the Creutzfeldt-Jakob disease (vCJD) (29).
- Cell banks, production cells and the large proteins produced are rigorously and regularly tested for the absence of viruses and other contaminants (Monograph on the Advate Product).
- The product is genetically designed from a CHO cell-line that is resistant to many human viruses, which was isolated before the emergence of many existing pathogens and which has been purified and tested through multiple phases of production (33).
- Furthermore, the production process includes several steps for viral removal and inactivation, including immune-affinity chromatography ion-exchange chromatography and solvent/detergent treatment (1).

TABLE 4

## CLASSIFICATION OF RECOMBINANT FVIII PRODUCTS

	FIRST GENERATION	SECOND GENERATION	THIRD GENERATION
Addition of protein of animal/human origin to the cell culture medium	Yes	Yes	No
Addition of protein of animal/human origin to the end product	Yes	No	No
Trade name	Recombinate	Kogenate FS Helixate FS ReFacto	Advate ReFacto AF

TABLE 5

SIGNIFICANCE OF PRODUCT CHARACTERISTICS	
PRODUCT CHARACTERISTIC	SIGNIFICANCE OF CHARACTERISTIC
Cell line from Chinese Hamster Ovary (CHO) used to grow the factor VIII	<ul style="list-style-type: none"> <li>• The CHO cell line used to produce Advate derives from a master cell bank, which therefore ensures the homogeneity of the cell population and its purity</li> <li>• Each fermentation begins with the re-animation of cells from the working cell bank, to ensure the integrity of the cell line</li> <li>• CHO is a thoroughly researched and characterized cell line and is therefore used in the production of many recombinant proteins.</li> <li>• CHO enables post-translation modifications of factor VIII to be carried out, to ensure the correct folding of the protein molecule</li> <li>• Improved safety through resistance to infections caused by most human viruses (Coronavirus, measles, influenza, herpes, rhinovirus etc.)</li> <li>• Not derived from tumor cells</li> </ul>
Culture medium	<ul style="list-style-type: none"> <li>• No components of human or animal origin used in the production process</li> <li>• The medium contains vegetable products, salts, amino acids, vitamins and sugars</li> </ul>
Purification without use of proteins	<ul style="list-style-type: none"> <li>• Murine hybridoma cell line used for the production of anti-FVIII monoclonal antibodies (Mab) suited to a vegetable medium without proteins</li> <li>• Viral inactivation using Solvent/Detergent S/D treatment (TNBP+TritonX-100/Tween 80)</li> </ul>
FVIII stabilizers used in final production phase	<ul style="list-style-type: none"> <li>• Absence of human or animal albumin in the stabilization process</li> <li>• Components used as a substitute for albumin               <ul style="list-style-type: none"> <li>• Non-protein stabilizer: Trehalose</li> <li>• Surfactant: Polysorbate 80</li> <li>• Loading agent: Mannitol</li> <li>• Reducing agent: Glutathione reductase</li> </ul> </li> </ul>

### ADVATE. SAFETY AGAINST THE DEVELOPMENT OF INHIBITORS

As has often been pointed out in the preceding chapters of this report, the appearance of factor VIII inhibitors is the most significant clinical complication in the treatment of Hemophilia A. The risk of developing inhibitors is greater in patients with severe Hemophilia A than in patients with moderate or mild Hemophilia A (35).

Taking into account the impact of the development of inhibitors on the clinical management and on the quality of life of hemophilic patients, the European Medicines Agency (EMA) recently held a meeting on the treatment of Hemophilia A and the development of inhibitors. At this meeting, a group of experts discussed the possibility of standardizing, internationally, the requisites to be fulfilled in the realization of clinical studies conducted on patients affected by Hemophilia A, in order to evaluate the

incidence of development of inhibitors to factor VIII (36, 37).

The existence of differences in the development of inhibitors among previously treated patients (PTPs) and among previously untreated patients (PUPs) is becoming ever more evident.

Following the board of experts, the EMA came to the conclusion that the appearance of inhibitors in PUPs is an immune reaction to an exogenous protein correlated to environmental and patient-intrinsic factors (the defect in the factor VIII coagulation gene, an immune-related genetic predisposition and family history) (36, 37). Contrastingly, the de novo development of new inhibitors in multi-transfused and stable PTPs, in whom intrinsic risk factors have thus been excluded, could reflect the neo-antigenicity of the infused FVIII. Due to the differences in the incidence of inhibitors between PTPs and PUPs, the EMA concluded that the immunogenicity of a specific product ought to be evaluated in patients suffering from severe Hemophilia A with a level of



TABLE 6

DEVELOPMENT OF INHIBITORS WITH ADVATE DURING CLINICAL AUTHORIZATION TRIALS (5)		
NUMBER OF PTPS TREATED WITH ADVATE	INHIBITORS OBSERVED DURING PILOT STUDIES	ESTIMATED RISK (95% CONFIDENCE INTERVAL)
198†	n=1	0.51% (0.03%– 2.91%)

† Based on a combined analysis of phase II/III and IIIb studies

TABLE 7

INHIBITOR DEVELOPMENT IN PTPS USING ADVATE (6)		
POPULATION	NUMBER OF PARTICIPANTS	INHIBITORS DEVELOPED
PTPs with FVIII $\leq$ 2%	402	2 recurring, low titer 1 de novo, low titer
PTPs with FVIII $\leq$ 2% without history of inhibitors	348	1 new-onset, low-titer inhibitor

FVIII < 1%, only among those patients who have previously been treated (PTPs), defined as patients with more than 150 exposure days' exposure to the treatment (36, 37). The EMA therefore concluded that it is not appropriate to carry out clinical studies on PUPs aimed at evaluating the risk of induction to the development of inhibitors linked to a product.

Following the EMA's guidelines, the results of various clinical studies have indicated a low incidence of inhibitors in PTPs with Advate.

### Clinical Studies on Advate (5)

In the clinical authorization trials carried out on Advate, only one case of low-titer inhibitor was reported (Table 6).

### Post-marketing studies carried out with Advate

Following the market launch of Advate, the PASS study (Post Authorization Safety Surveillance) was begun in order to record long-term efficacy during routine clinical practice and to monitor for the appearance of inhibitors (6). The PASS study is the largest single post-marketing study ever conducted for a product based on FVIII. Patients were

enrolled independently of both their treatment history (PTP/PUP) and of their record of the presence of inhibitors; 541 patients were enrolled in October 2007; 521 were treated with Advate and of these 88% were PTPs (6). The number of inhibitors reported in the PTP population, in line with the EMA's indications, is reported in the table below (Table 7).

Based on these clinical studies and the data from routine practice, the immunogenicity profile of Advate appears extremely favorable compared to other FVIII-based products, and especially compared to that of BDD-FVIII products, for which the literature reports high rates of inhibitor development (38, 39).

### ADVATE. ADVERSE EFFECTS

Table 8 reports the type and frequency of adverse reactions observed with Advate during the clinical trial studies (34). Frequency categories were evaluated on the basis of the following criteria: very common ( $\geq$ 1/10), common (from 1/100 up to <1/10), not common (from 1/1 000 up to <1/100), rare (from 1/10 000 up to <1/1 000) and very rare (<1/10 000), not known (the frequency cannot be calculated from the available data).

Within each frequency category, adverse

TABLE 8

## FREQUENCY OF ADVERSE REACTIONS WITH THE DRUG IN CLINICAL STUDIES

SYSTEM CLASSIFICATION ACCORDING TO MEDDRA TERMINOLOGY	ADVERSE REACTIONS	PATIENTS	FREQUENCY ADVERSE EXPERIENCES (% PATIENTS) <sup>A</sup>	FREQUENCY <sup>B</sup>
Infections and infestations	Influenza	1	0.43	Not common
	Laryngitis	1	0.43	Not common
Blood and lymphatic system disorders	Lymphangitis	1	0.43	Not common
Nervous system disorders	Headaches	5	2.14	Common
	Dizziness	3	1.28	Common
	Memory disturbances	1	0.43	Not common
	Tremor	1	0.43	Not common
	Migraine	1	0.43	Not common
	Dysgeusia	1	0.43	Not common
Eye disturbances	Inflammation of the eye	1	0.43	Not common
Vascular disorders	Hematoma	1	0.43	Not common
	Flushes	1	0.43	Not common
	Paleness	1	0.43	Not common
Respiratory, thoracic and mediastinal disorders	Dyspnea	1	0.43	Not common
Gastrointestinal disorders	Diarrhea	2	0.85	Not common
	Upper abdominal pain	1	0.43	Not common
	Nausea	1	0.43	Not common
	Vomiting	1	0.43	Not common
Skin and subcutaneous tissue disorders	Itching	2	0.85	Not common
	Exanthema	2	0.85	Not common
	Hyperhidrosis	1	0.43	Not common
	Diaper dermatitis	1	0.43	Not common
Systemic disorders and conditions related to the administration site	Fever	3	1.28	Common
	Peripheral edema	1	0.43	Not common
	Chest pain	1	0.43	Not common
	Shivering	1	0.43	Not common
	Feeling of strangeness	1	0.43	Not common
Diagnostic tests	Positivity of anti-factor VIII antibodies	5	2.14	Common
	Increased levels of alanine aminotransferase	1	0.43	Not common
	Lowered level of coagulation factor VIII <sup>b</sup>	1	0.43	Not common
	Drop in hematocrit level	1	0.43	Not common
	Laboratory tests not within norm	1	0.43	Not common
Traumatism, poisoning and procedure complications	Post-intervention complication	1	0.43	Not common
	Post-intervention hemorrhage	1	0.43	Not common
	Local reaction to intervention	1	0.43	Not common

a) Percentage of patients calculated on the basis of the total number of patients (234)

b) A sudden drop in clotting factor VIII levels occurred in one patient during continuous infusion with Advate, following a surgical intervention (10-14 days post intervention). Hemostasis was constantly maintained during this period. Both terms of factor VIII plasma level and clearance percentages were back to normal by the 15th post-operative day. Tests for factor VIII inhibitor conducted both after completion of continuous infusion and at the end of the study returned negative results.

TABLE 9

SIGNIFICANCE OF THE NON-CLINICAL PROPERTIES OF ADVATE	
PROPERTY	SIGNIFICANCE OF PROPERTY
'Needle-free' reconstitution device for simpler reconstitution	Advate is available with the practical reconstitution system BAXJECT II, a needle-free device that enables the product to be mixed in a safer, faster and simpler way. The solvent is added to the freeze-dried powder in a single aseptic procedure. This shortens drug-preparation time and facilitates the reconstitution process for the patient or their carer.
Constant supply and quality of recombinant factor VIII (rFVIII) products	<p>A critical issue for hemophilic patients is the trustworthiness of their supply of factor concentrate. Advate is a product that uses the most recent recombinant technology available today, using CHO cells isolated from a master cell bank that is completely independent of products of human origin in every phase of its production. The risk of transmitting blood-borne pathogens is thereby eliminated. This also means that the supply of Advate is independent of the collection of plasma from donors.</p> <p>Plasma-sourced concentrates, on the other hand, depend on a constant supply of plasma originating from donors that may be influenced by a variety of political and/or economic factors. Furthermore, they require precise methods of purification and storage in order to show up any known pathogens.</p> <p>The Scientific Committee of the EMA has stated the following about Advate: "Careful type-approval of the production process of the pharmacological substance on a commercial scale demonstrated a production of the pharmacological substance itself to be of a consistent and comparable quality at both sites used for production. The pharmacological substance was amply characterized, demonstrating the equivalence of batches both on pilot and on commercial scales, using the latest technology. Viral security was also demonstrated against encapsulated viruses" (1).</p>
Six-month storage period at room temperature	Advate can be stored at room temperature for 6 months, thus offering greater flexibility and practicality for patients and thereby leading to improved compliance. Compliance is an important parameter to consider when deciding on a treatment for persons affected by hemophilia, as there is a close relationship between compliance and the frequency of bleeding episodes (2). Furthermore, Advate's longer storage time at room temperature can also reduce product waste due to patients' storage habits, which may often vary during routine practice.

effects are listed in descending order of severity.

As with other products for intravenous administration, allergic hypersensitivity reactions were reported with Advate, including anaphylactic/anaphylactoid reactions (unknown frequency).

Advate. Non-clinical product properties

Hemophilia A is a lifelong chronic pathology with severe repercussions on the patient's life. Consequently, advantages linked to the practical application of the product, which can alleviate the load on the patient in terms of managing the disease, could increase compliance with treatment and, consequently, bring about an improvement in clinical results (2). The practical advantages of Advate are summarized in Table 9.

Advate is available in the largest range of dosages of any of the rFVIII products. Currently on the market are six different formulations in

single-dose phials, all of them to be reconstituted in 5 ml of sterile water (see Table 10).

By supplying the widest choice of formulations, Advate offers greater flexibility and precision to physicians while reducing inconvenience to patients, allowing the drug to be infused by means of a single phial.

## CONCLUSION

The treatment of hemophilia requires a multi-factored approach that, efficacy aside, must encompass viral safety, immunogenicity and the practicalities of the treatment itself.

On the market since 2004, Advate remains today the only full-length-molecule recombinant FVIII produced entirely without human or animal plasma proteins.

TABLE 10

## FORMULATIONS OF ADVATE IN SINGLE-DOSE VIALS (1)

FORMULATION	RECONSTITUTION VOLUME
250 IU	5ml
500 IU	5ml
1 000 IU	5ml
1 500 IU	5ml
2 000 IU	5ml
3 000 IU	5ml

Advate guarantees to the patient the maximum safety level against the transmission of blood-borne pathogens, both known and unknown.

Advate's clinical efficacy has been widely demonstrated in every clinical context through a vast pre- and post-regulatory clinical development plan involving a large number of patients.

Advate's molecule, octocog alpha, is a full-length molecule, completely analogous to native FVIII. Evidence exists to show that such a chemical structure confers on Advate clinical features that are virtually identical to those of native FVIII. This structural integrity of the active principle could be a determining factor for the low immunogenicity of Advate, amply

demonstrated by the findings of the clinical development plan and recently confirmed in PTPs in the Advate PASS post-marketing surveillance study.

Further to this, thanks to the wide range of formulations available and to the possibility of storage at room temperature for up to 6 months, Advate shows clear practical advantages for a patient-centered therapy that can meet the needs of each individual user.

In view of the above and in response to patients' requirements, Advate is the most advanced therapeutic option, guaranteeing to hemophiliacs full viral safety, maximum efficacy, low immunogenicity and remarkable ease of use.

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## 5. Advate in the treatment of Hemophilia A: Cost-effectiveness assessment of on-demand treatment vs. prophylaxis, based on the product's half life

*Stefano Capri, Walter Ricciardi*

### INTRODUCTION

In previous chapters, it was emphasized how treatment of hemophilia requires the infusion of clotting factors over the patient's entire lifespan. In Chapter 3, which was concerned with the resources deployed for hemophilia, it was pointed out that, due to the high cost of such treatment, especially for latest-generation products, and therefore those most highly evolved such as Advate, it is necessary to compare drug efficacy with its cost to the National Healthcare System (the Italian SSN).

Taking the safety and efficacy of Advate into consideration, as described in previous chapters, the present section is aimed at comparing two treatment strategies with the help of a cost-effectiveness assessment. As previously stated, the two currently available strategies are, on the one hand, on-demand treatment, i.e., the administration of the deficient factor during a bleeding episode in order to limit the severity of its consequences and bring about its resolution, and, on the other hand, prophylaxis. In the case of the latter, primary prophylaxis provides for continuous administration of the deficient factor after the first episode of intra-articular bleeding, and before the second year of life (see Chapter 2).

Before embarking on an economic assessment of pharmaceutical technology for such a rare disease as hemophilia, on a population of approximately 4 000 patients and a prevalence of 5/100 000, it is necessary to review some methodological considerations. Cost-effectiveness assessments are not usually called upon in the case of rare diseases, as the criterion for resource allocation is that of 'rescue', to be understood as the implementation of available

treatments in order to reduce the hardships of the few patients affected by a disease which is usually chronic and difficult to treat or cure. In the case of hemophilia, economic assessments have been carried out only recently (see the final part of this chapter for a short overview), especially after the introduction of second and third generation recombinant factor VIII, which is more expensive than previously used plasma-derivatives. However, due to their superiority in terms of effectiveness and especially safety, economic comparisons are limited to the two treatment strategies mentioned above, rather than to a comparison of different clotting products.

Nonetheless, interest in economic assessment is growing also in the case of rare diseases. The National Institute for Health and Clinical Excellence (NICE) has produced a draft document, which is still to be completed, in order to provide guidelines for assessments in this domain (1). The main conclusions are the following: the Incremental Cost-Effectiveness Ratio (ICER) for orphan drugs may reach a value ten times higher than the threshold value accepted for the drugs normally used for widespread diseases. The terms of reference for a new orphan drug should therefore be the value attributable to orphan drugs already available on the market and the final cost per Quality Adjusted Life Year (QALY) should not be weighed against equity-related parameters (in short, rarity should not be rewarded: it should not be given privileged consideration compared to the high prevalence of more common diseases).

In any case, it would appear that a high degree of caution is called for when carrying out economic assessments in the field of rare diseases, because the application of economic

methods to this area still entails issues of methodology and application (2).

A basic concept in the economic assessment of hemophilia is the patient's quality of life. The considerable impact of treatment on patient quality of life has been extensively dealt with in previous sections: without appropriate treatment, the patient risks bleeding, joint damage and, in some cases, premature death. Furthermore, it should not be disregarded how in the past the use of plasma-derivatives with critical safety characteristics caused HIV, hepatitis B and C infections in many patients all over the world and led to thousands of deaths. The costs incurred were not just economic ones: social costs were also very high (3). The economic assessment of different strategies, moreover, is aimed at making evidence available to decision-makers who manage public resources, in an attempt to combine economic effectiveness with therapeutic efficacy. This is why the two strategies compared by the present economic assessment both use a cutting edge product: Advate.

The evidence presented in Chapter 2 shows how primary prophylaxis is an advantageous alternative to on-demand treatment because it prevents the occurrence of hemorrhaging along with their collateral effects on the joints, helps reduce the number of hospitalizations and increases the patients' quality of life. However, given that the consumption of clotting factor is higher with prophylaxis, the aim of this chapter is to quantify its impact on total healthcare expenditure, taking into account how, on the one hand, treatment costs will increase, and on the other, resources will be saved thanks to the prevention of bleeding episodes and therefore of treatment, with a probable increase in quality of life and patient survival.

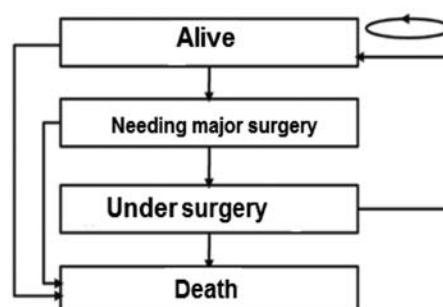
## METHODS

The cost-effectiveness analysis was based on the Incremental Cost-Effectiveness Ratio (ICER) indicator, to be understood here as the added cost per unit gain in QALY, which is incurred by one treatment strategy when compared to the other. In this case, the two strategies are the prophylactic treatment of Hemophilia A using infusions of factor VIII Advate on the one hand, and on-demand treatment using infusion of the same factor. Given the fact that both strategies refer to the entire lifespan of the patient, the study design could not be other than that of a model. We therefore adopted a model previously designed by Markov, which was created and used for the UK (4, 5) and which had been adjusted to the Italian setting with the costs described in Chapter 3 of the present report. The model simulates the entire lifespan of 100 patients, each of whom might find him/herself in one of the following four states over time: alive; in need of major surgery; undergoing surgery; deceased. All individuals enter the model in the 'alive' state at birth; in the subsequent cycle, they can either remain in the previous state ('alive') or they can move to the state where they need major surgery or to the 'deceased' state. In the following cycle, those who were in the 'in need of major surgery' state move either to the 'under surgery' state or to the 'deceased' state. After surgery, individuals can either go back to the 'alive' state or to the absorbing state of 'deceased' (Figure 1). Each cycle was deemed to last one year.

In order to ensure complete consumption of resources and of benefits, i.e., total use of

FIGURE 1

### THE MARKOV MODEL STATES





life years, the time horizon was extended to 70 years.

Life expectancy for hemophiliacs was assumed to overlap that of the general population, in patients affected neither by HIV nor by hepatitis C (6). Given the post-surgical complications caused by the increased tendency to bleed, mortality in the first year after surgery was increased by 1% over that normally encountered. In order to calculate the probability of having to resort to surgery, undergo outpatient examination or additional hospital examination, various rates that have previously estimated in the literature were used (6).

The model encompassing different probability alternatives is illustrated in Figure 2; only the prophylaxis arm is shown. This is identical to the on-demand arm, the only difference being that some values concerning the probability of particular events and treatment costs change, due to differences in frequency of administration and of dosage.

In Chapter 2, which dealt with treatments, it was stated that the prophylaxis protocol recommended by the World Federation of Hemophilia (WFH) consists in the infusion of 25-40 IU/kg of factor VIII, three times a week. However, this model computes an actual dosage based on the amount of factor VIII needed to prevent clotting factor levels from dropping below 1 IU/dl. As suggested in the WFH Guidelines, this is a threshold value for clinically effective prophylaxis (see Chapter 4). To this end, bolus amounts were computed thanks to a model correlating initial *in vivo* concentration at time 0 with the amount requested at time t after infusion, taking the half-life of the product used into account. The model for estimating resulting dosages is described by Miners et al. (4), with further references to the original author.

In order to determine the dosage of the on-demand alternative, a bolus amount of 31 IU/kg was assumed. This amount was deemed sufficient to arrest bleeding in patients affected by severe hemophilia.

The costs, which have already been described in Chapter 3 of the present report, are expressed in 2010 Euros and are based on the Diagnosis Related Group (DRG) code 209 for surgical procedures and on outpatient tariffs for check-up examinations. The cost of rFVII Advate was quantified as €0.75 per IU, to be understood as the sale price to the National Healthcare System.

In order to compute the utility associated with the 'alive' and 'under surgery' states, a distinction was made between patients subjected to on-demand treatment and those subjected to prophylaxis, based on a study by Miners et al. (7), which showed that utility is lower in patients affected by severe hemophilia compared to those affected by moderate/mild hemophilia. These values decrease, however, with age in both groups. The utility for on-demand patients was assumed to equal that for patients affected by severe hemophilia who had never been subjected to primary prophylaxis, while for patients subjected to prophylaxis, utility was assumed to equal that for patients affected by moderate/mild hemophilia.

Unlike the original model, in this case indirect costs - that is, the loss of economic productivity associable with the patients' condition - were not included, because no relevant data is available for Italy.

Therefore, the analysis was carried out from the point of view of the National Healthcare System (the Italian SSN).

All values, regarding both costs and effectiveness (QALY), were discounted by 3%, according to the guidelines suggested for the Italian setting (8, 9) and as applied extensively in the literature.

## RESULTS

The strategy of using Advate in primary prophylaxis proved more effective than the on-demand strategy, with both approaches using the same technology. Indeed, over the patient's whole lifespan there was a mean gain of 6.28 QALYs (21.56 against 15.28). These values have been discounted: that is, the actual gain is 14.57 QALYs (45.49 against 30.92). The costs of the prophylaxis strategy are higher by €220 000 (discounted values), measured over the patient's entire lifespan. Therefore, the ICER obtained comes out at € 35 036 (Table 1). This value is only just over the € 30 000 value, which, in the absence of any values set down by the regulatory authorities or HTA agencies in Italy, appears to be the one adoptable as a threshold of acceptability. However, it should be borne in mind that, hemophilia being a rare disease, the value of € 35 036 per QALY gained is particularly modest. Previous economic assessments for orphan drugs have found significantly higher values. For example, the above-cited NICE (1)

FIGURE 2

REPRESENTATION OF THE 'PROPHYLAXIS' ARM OF THE MARKOV MODEL

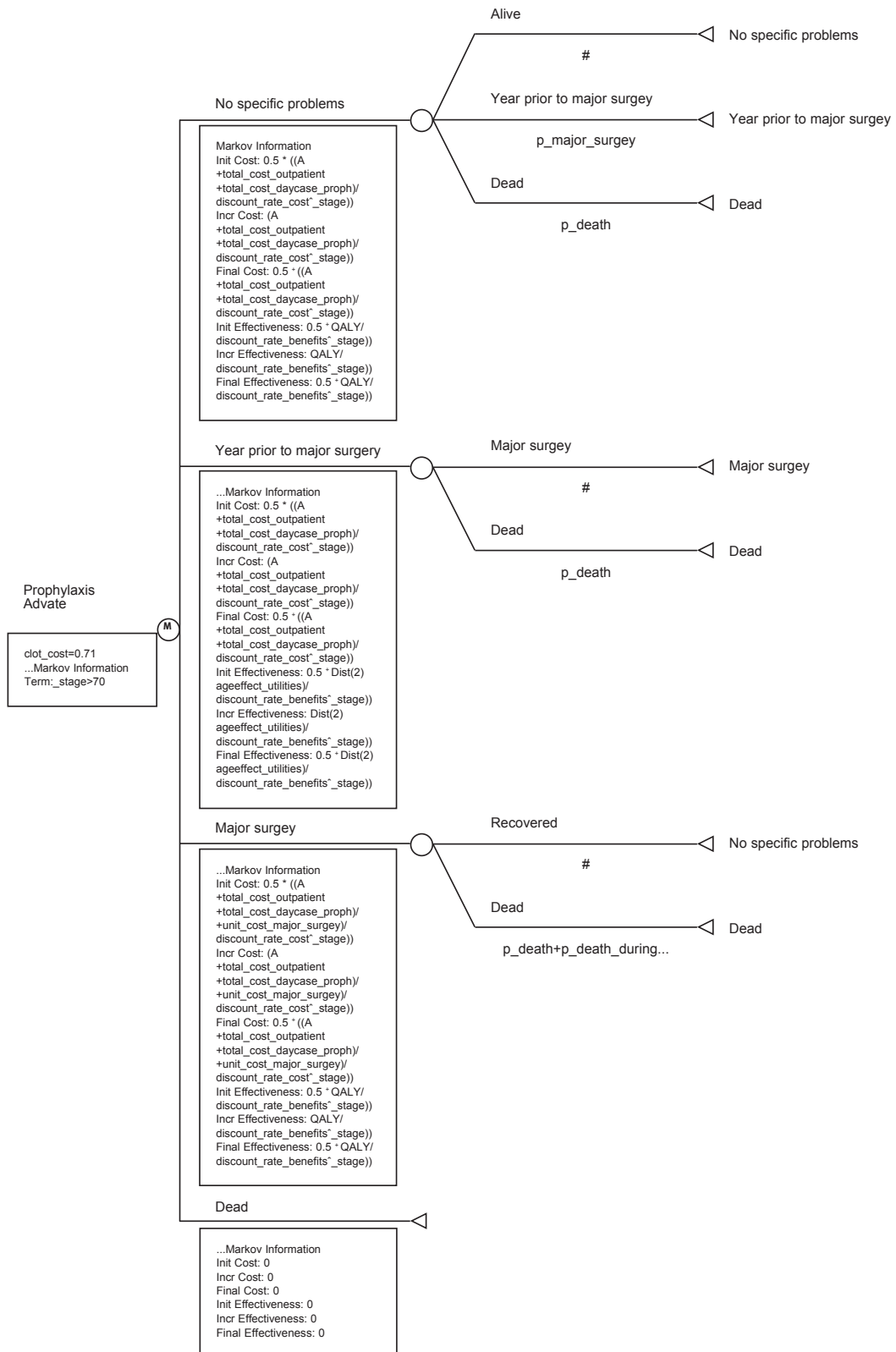


TABLE 1

## COSTS, QALYs AND ICER IN THE PROPHYLAXIS VS. ON-DEMAND COMPARISON: BASELINE CASE

STRATEGIES	COST	QALYs	DIFFERENTIAL COSTS	DIFFERENTIAL QALYs	ICER
ON DEMAND	1 329 385	15.28			
PROPHYLAXIS	1 549 323	21.56	219 938	6.28	35 036

document on orphan drugs reports ICER values ranging from £23 000 to £391 000, with a mean value of approximately £206 000.

In order to test the soundness of the results obtained, a probabilistic sensitivity analysis was carried out. 10 000 interactions were implemented using the Monte Carlo method: interactions are shown on an acceptability curve (Figure 3).

An ICER value of €30 000 has a probability of occurring in 45% of cases, while a value of €70 000 will occur in 92% of cases.

A high level of uncertainty is therefore associated with a baseline-case result of €35 036, a value with a probability of 60%. However, with a 95% probability of an ICER of €90 000, and considering that this is a rare disease, the prophylaxis strategy with Advate attains a favorable assessment in comparison with other technologies.

## DISCUSSION

The cost-effectiveness value is very similar to the one obtained for the UK using the same model (5), of £38 000. At the moment, no other economic assessment studies appear to have been published with which a direct comparison can be made. There are, in fact, two studies comparing prophylaxis and on-demand treatment, although the models used differ considerably. The European study by Lippert et al. (10) was based on a decision analysis model; it extrapolated data from a clinical study which extended over one year and the time horizon for the cost-effectiveness analysis was of an equal duration. With such a short time horizon, it comes as no surprise that ICER values are significantly higher than in a lifetime model. Drawing a distinction between patients older than 30 and patients younger than 30, affected by HIV and not, the study found that ICER values, in terms of cost per QALY gained, range from €1 236 982 to €4 766 366 in Germany, of €5 744 120 in Sweden,

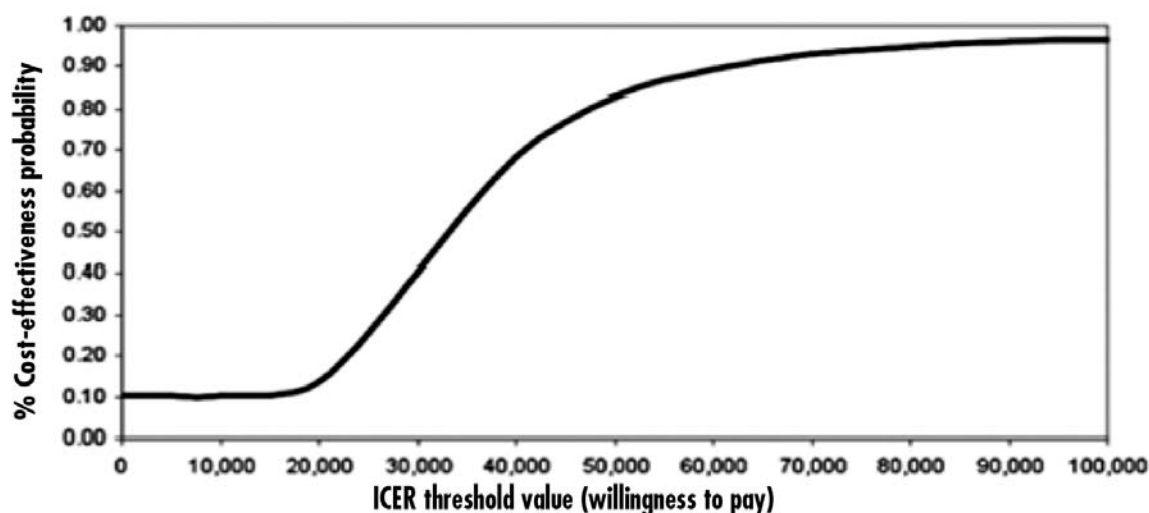
(in some cases, prophylaxis is overtaken by on-demand treatment, i.e., on-demand treatment would result as more effective and less expensive in these cases), from €1 284 061 to €4 402 834 in the Netherlands and from €1 731 820 to €5 688 753 for the UK. Looking beyond the differences in the designs of different models, the underlying reason for the considerable discrepancies in ICER values found compared to the data obtained with the present economic assessment is to be sought in the difference in time horizon. With a horizon of just one year, gains in terms of QALY cannot be anything but minimal: more precisely, they range from 0.0187 to 0.0586 QALY<sub>s</sub> according to the specific case, with an annual difference in costs amounting to some tens of thousands euros. This finding would therefore appear to be consistent with the one given immediately above.

Another study (11), based on “escalating dose” prophylaxis over a 5-year time horizon for Canada, found slightly lower ICER values of CAN\$ 542,938. When standard prophylaxis is applied, ICER exceeds CAN\$1 000 000. In this case too, previous considerations regarding the duration of the simulation apply. However, a distinction must here be made: in the Canadian study, ICER comes out at approximately one tenth of the mean value found in European studies, with a ten-fold higher differential for QALY, of 0.31. There would therefore appear to be a certain similarity in structures between these two models. It will therefore be important for future studies to analyze the models currently proposed in the literature more thoroughly, determining their limitations and benefits and finding ways of suggesting new models which better reflect the actual treatment and consumption of resources in individual countries.

As mentioned in the Methods section, the model used here is characterized by a mechanism based on estimating the requirement for factor VIII which is connected to the half-life of the product used. It was according to these assumptions, already extensively described in Chapter 4 of the present report, that the same

FIGURE 3

ACCEPTABILITY CURVE FOR THE PROPHYLAXIS STRATEGY WITH ADVATE® (FOR EACH ICER THRESHOLD VALUE ON THE X-AXIS, THERE IS A CORRESPONDING ASSOCIATED PROBABILITY ON THE Y-AXIS)



model has recently been used to compare not two different strategies, but two different third-generation products, Advate e Refacto AF®, while using the same prophylaxis strategy (12).

Because the half-life of Refacto AF® appears to be shorter than that of Advate®, the authors assumed that in order to achieve the same efficacy, Refacto AF® should be administered in greater quantities. Through the cost minimization obtained, it is thus found that although Advate costs the National Health System 8% more than Refacto AF® (€0.75 per IU compared to €0.69 per IU), prophylactic treatment with Advate would bring savings of 58% (Figure 4).

The hypothesis of differentiating efficacy according to the product's half-life obviously requires further grounding and has been mentioned here only to complete our analysis.

A complete economic assessment of hemophilia treatment cannot fail to look at costs of therapy where the patient develops inhibitors (immunogenicity).

This condition was covered in Chapters 2 and 3, both under the profiles of clinical management and of resource allocation. Immune tolerance induction (ITI), which is the treatment of choice where inhibitors develop, requires the administration of high doses of FVIII with high frequencies and over a long period of time, at least 12 months, with the aim of eradicating the antibody (see Chapters 2 and 3).

As the probability of adopting an ITI regime is closely intertwined with the immunogenicity

of the product used, alongside treatment costs, future economic assessments of immune tolerance will have to include the immunogenic profile of the actual product used.

Chapter 2 stresses how, according to the requirements imposed by the EMA, the risk of developing inhibitors that is linked with a specific product must be assessed on previously treated patients (PTPs).

As Chapter 3 points out, the post-authorization safety surveillance study (PASS) on Advate, whose study population was exposed for over 50 days, and whose factor VIII was lower than or equal to 2% without a history of inhibitors, found a *de novo* inhibitor incidence of 0.29% (95% CIs 0.01%–1.59%) (13).

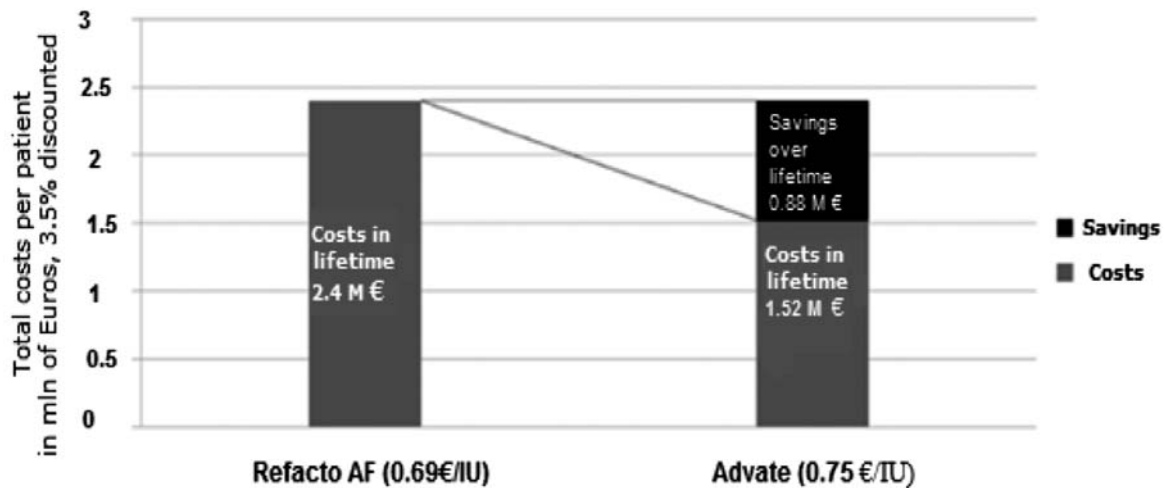
This data, which reflects favorably on Advate, suggests a lower probability of adopting ITI and, consequently lower costs for the National Healthcare System. These considerations highlight the urgent need to carry out a comprehensive assessment of these economic implications on the National Healthcare System in its treatment of hemophiliac patients with inhibitors.

## CONCLUSION

Prophylaxis with Advate is far more effective than an on-demand strategy using the same technology and at a reasonably higher cost. Indeed, on average nearly 15 QALYs per

FIGURE 4

## TOTAL COSTS PER PATIENT OF PROPHYLACTIC TREATMENT WITH ADVATE® AND WITH REFACTO AF®



patient (discounted value 6.28) are gained over the patient's entire lifespan.

The ICER value of prophylaxis using Advate equals €35 036, which comes within the range of acceptable values, especially taking into consideration that hemophilia is a rare disease. However, this value is quite uncertain, with a high probability of exceeding the value of €70 000. The ICER value is comparable to that obtained for the UK: £38 000 (5).

The complex mechanisms underlying these models and the assumption of some hypotheses that still await confirmation, such as the impact of the different (factor VIII) half-lives of the different technologies used, render further economic assessment necessary in order better to estimate the impact on efficacy and costs, possibly by breaking data down according to category of patient and severity of disease, and employing different model architectures.

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## 6. The use of Advate in Hemophilia A treatment: impacts on organization and management, finance and quality of life

*Maria Lucia Specchia, Silvio Capizzi, Flavia Kheiraoui, Maria Assunta Veneziano, Chiara de Waure, Giuseppe La Torre, Walter Ricciardi*

In order to assess the organizational and management impact of using Advate for the treatment of Hemophilia A, the present chapter sets out to analyze the Italian treatment context and the value of the pharmaceutical product by investigating aspects under the following headings:

- The salient features of national and regional hemophilia registries;
- Organization and activities of the centers for the diagnosis and treatment of hemophilia;
- Prophylaxis;
- Home care services;
- Patients' quality of life.

These aspects were inspired by the principles of the rules published and adopted in 2008 by the European Commission, aimed at ensuring a minimum level of care, therapy and treatment for hemophilia. This document, entitled "European principles of hemophilia care" contains the key principles of comprehensive hemophilia care on which care for hemophiliacs should be based (Figure 1) (1, 2).

### NATIONAL AND REGIONAL HEMOPHILIA REGISTRIES

For rare and chronic diseases such as hemophilia, pathology registries are vital instruments for national healthcare systems. As stated by the World Health Organization (WHO) during a joint summit with the World Federation of Hemophilia (WFH) in 1997, such registries take priority in any interventions aimed at improving management of these diseases.

Potential benefits that may derive from a national hemophilia registry include the following:

- Provision of evidence on the number of patients and their needs;

- Planning support for service provision and for hemophilia centers;
- Effective and efficient allocation of resources for the treatment of the disease;
- Improvement of the supply and distribution of coagulation factor concentrates;
- Satisfaction of the information requirement of all stakeholders and support for the network of professionals and other actors;
- Monitoring of the onset of adverse events (infections, inhibitor development) and health trends and outcomes in hemophiliac population;
- The provision of data for research (3).

The template for all such registries is supplied by the National Hemophilia Database (NHD), created by the United Kingdom Haemophilia Centre Doctors' Organisation (HKHCDO). The Registry was set up in the United Kingdom in 1967, on the occasion of recognition of Hemophilia Centers by the Department of Health (4). Information flow relies on a web-based system; registry data enables users to identify new diagnoses, deaths, coagulation factor consumption, and to monitor adverse events (such as inhibitor development, hepatitis and HIV-related viruses etc.). Furthermore, periodic reports are published on treatments and outcomes, which serve as a database for *ad hoc* research groups (5, 6).

In 1988, the Canadian Hemophilia Registry was established with the aim of monitoring the number of patients affected by hemophilia. Data derived from Canadian hemophilia centers currently also include patients affected by Von Willebrand disease and by other rare coagulation diseases. Furthermore, the database provides data for epidemiological surveillance and the development of research

FIGURE 1

## THE EUROPEAN PRINCIPLES OF HEMOPHILIA CARE (2)

**EUROPEAN PRINCIPLES OF HAEMOPHILIA CARE**

We call upon European and national healthcare policy makers to join us in taking strong and decisive action to ensure that people with haemophilia have access to safe treatments and optimum care throughout Europe. We endorse the following Principles, as elements of haemophilia care provision that should be available in each European Country:

**1. A Central Haemophilia Organisation with Supporting Local Groups**

In each country there should be a central organisation for haemophilia care supported by centres operating at the local level. These organisations should be responsible for accurate record keeping and the effective administration of haemophilia care. Such an approach also facilitates the exchange of best practice and the coordination of research.

**2. National Haemophilia Patient Registries**

Each country should have a national haemophilia patient registry administered by the central haemophilia organisation. Patient registry data can be used to facilitate resource planning and allocation, as well as provide accurate data on patient numbers, prescribing patterns, geographical spread and adverse events.

All registers should be held with suitable attention to confidentiality, national regulations and local best ethical practice.

**3. Comprehensive Care Centres and Haemophilia Treatment Centres**

Comprehensive Care Centres and Haemophilia Treatment Centres should be established to ensure that people with haemophilia have access to the full range of clinical specialties and appropriate laboratory services.

**4. Partnership in the Delivery of Haemophilia Care**

Clinicians and patient representatives should be part of national and/or regional haemophilia care decision making in partnership with ministries of health and social affairs, as well as those organisations that deliver haemophilia care via a formal mechanism such as a National Haemophilia Co-ordinating Group.

**5. Safe and Effective Concentrates at Optimum Treatment Levels**

People with haemophilia need to have access to safe and effective treatment at optimum levels. This improves physical health, life expectancy and quality of life and reduces the psycho-social and economic impact of this bleeding disorder on the patient and his/her family. It also reduces the amount of long-term support needed from healthcare provider resources.

**6. Home Treatment and Delivery**

Home treatment and home delivery should be available in each country to facilitate immediate and effective treatment. This results in a reduction in hospital visits, prevents short and long-term disability and allows children and adults with haemophilia to have the freedom to lead lives that are as normal as possible.

**7. Prophylaxis (Preventative) Treatment**

Prophylaxis treatment should be available to people with haemophilia as it has been shown to prevent and improve chronic joint disease. Prophylaxis also promotes health and social well-being and reduces the burden of the condition.

**8. Specialist Services and Emergency Care**

Haemophilia care requires the co-ordination of a number of services to make sure that the particular needs of those with haemophilia are met.

In critical situations, people with haemophilia need immediate access to treatment as well as to skilled care through Accident & Emergency departments and to the range of specialists required to ensure their safety.

**9. Management of Inhibitors**

Some people with haemophilia develop "inhibitors", when their bodies inactivate the replacement clotting factor treatment. Those affected need to have immediate access to optimum treatments. Where appropriate, immune tolerance induction therapy (ITT) and the management of bleeding should be administered by clinicians with the necessary expertise, in hospitals with appropriate clinical and laboratory resources.

**10. Education and Research**

Recruitment and education of physicians in the area of thrombosis and haemostasis is an important task for the future to secure high quality care. Further research into haemophilia is also required, with priority areas for investigation being modified factor VIII and IX agents with longer half-life, less immunogenicity, new administration techniques, better understanding and prevention of the development of inhibitors and gene therapy. Other areas of research are required to further the development of care for patients and families, including examination of different service delivery models, outcomes and quality of life measures.

projects, e.g., the monitoring of viral infections and causes of death among the population of patients affected by coagulation diseases (7).

In the same year (1988), the National Registry of Congenital Coagulation Disorders (*Registro Nazionale delle Coagulopatie Congenite* - RNCC) was established at the Italian Supreme Healthcare Institute (*Istituto Superiore di Sanità* - ISS); this registry has the objective of monitoring the spread of HIV and hepatitis C-related viruses among the population of patients affected by Hemophilia and other coagulation disorders, following the infusion of plasma-derived clotting factor concentrates that had not been subjected to viral inactivation (8-10). This Registry remained active until 1999 (6).

In 2003, the Italian Association of Hemophilia Centers (*Associazione Italiana Centri Emofilia* - AICE) set up its AICE Registry of Congenital Coagulation Diseases, a database containing all data on patients affected by coagulation disorders, collected with the help of the Emocard patient-management software. During its half-yearly updates, the AICE database gathers data from Italian Hemophilia Centers.

Apart from personal details, the database also contains clinical information collected during the provision of hemophilia care (11, 12).

Over recent years, Emocard software has been enhanced through the creation of a new web-based platform called Emoweb, which is currently being activated in Hemophilia Centers all over Italy.

Emoweb enables the AICE database to be updated in real time, with direct data access restricted to physicians and patients. Furthermore, in 2001 the ISS established the National Registry of Rare Diseases, a branch of the National Network of Rare Diseases, with the aim of collecting a minimum amount of shared information regarding all rare diseases, including coagulation disorders. The information collected include whether the patient is living, diagnosis, name of the facility where the disease was diagnosed, date of commencement of the disease, date of diagnosis, and supplied (13).

Also in 2003, the Regional Registry of Congenital Bleeding Diseases was set up by the Emilia Romagna Region, coordinated by the Hospital Care and University Unit of



Parma, the Hub Centre of the Congenital Coagulation Disorder Network (14). The Register's web-based data flow is entirely financed by the Emilia Romagna Region and can be consulted on a dedicated website ([www.registroemofiliarer.it](http://www.registroemofiliarer.it)). Not only does the Registry provide epidemiological data, providing the ability to monitor the disease and its complications, it also enables the user to monitor treatment regimes, hospitalizations and surgical procedures. Furthermore, the Registry allows the quality of care provided by the Hemophilia Centers and Healthcare Units to be promoted and verified. Data quality is ensured both at source, thanks to the use of computerized patient medical records, and by checks carried out by the Parma center (15).

Finally, in 2005, with the aim of developing a detailed database of congenital and acquired coagulation disorders, the RNCC was established in collaboration between the ISS Transfusion Methodology Department (Department of Hematology, Oncology and Molecular Medicine) and AICE. The RNCC contains data on the prevalence of various disorders, complications, requirements and drug consumption. The project was implemented with the help and active participation of the Federation of Hemophilia Associations (FEDEMO) (6).

In previous chapters of the present report, it has been shown how the treatment of patients with hemophilia requires a multi-disciplinary healthcare approach with high levels of complexity of care and consumption of resources. For this reason, updated knowledge of the epidemiology of various forms of coagulation disorders, the monitoring of treatment regimes, hospitalizations and surgeries in the various regions and on the national scale, are vital aspects of the provision and planning of healthcare programs (1). There should therefore be encouragement of the future implementation of measures aimed both at strengthening the instruments for data collection and securing information flows, and for processing and monitoring the quality of data gathered.

## ORGANIZATION AND ACTIVITIES OF CENTERS FOR THE DIAGNOSIS AND TREATMENT OF HEMOPHILIA

In Italy, the competent bodies for management of Hemophilia are Specialized Centers distributed across the national territory

(Figure 2). From the administrative point of view, these centers are recognized by specific regional decrees (see Appendix: List of Hemophilia Centers).

As it has been made clear in previous sections, Hemophilia A requires specific skills in the diagnosis and management phases as well as targeted treatment and high-intensity care programs. For this reason, the National Healthcare Service (Italy's SSN) needs a well-articulated organization, especially with regard to the activities within Hemophilia Centers, and rational use of resources.

Medical examinations and laboratory analyses required to determine the diagnostic picture of the disease are carried out on patients and on their relatives in the Hemophilia Centers. Most patients initiate contact with the Centers as infants, thanks to referrals by hospital neonatology or pediatrics units and by their general practitioners (GPs).

In general, pediatric patients have to undergo hematology check-ups on a quarterly basis, but sometimes this is done monthly. It is during the first years of life that prophylaxis treatment is started; in this phase, it is necessary to focus especially carefully on assessing efficacy and on checking for possible complications, including the development of inhibitory antibodies.

Adult patients need to undergo periodical multidisciplinary check-ups, at least once a year, and specialized examinations, customized according to clinical requirements. Check-ups are the core of the multidisciplinary approach to treating hemophilic patients of any age; it is one of the leading assistance activities carried out by a Center.

Check-ups should include general, hematochemical, virology and coagulation examinations, plus a joint examination carried out by a specialized team (a hematologist, an orthopedic specialist, a physiotherapist, etc.).

This joint examination should include:

- A general internal medicine health status assessment and assessment of specific conditions, with the booking of further examination if such are deemed necessary;
- Hematological assessment based on coagulation analysis, assessment of treatment appropriateness and check of the infusion journal;
- Orthopedic assessment and examination of target joints and of muscle tone and trophism;
- Postural assessment, in case a rehabilitation or physical therapy program, is necessary.

FIGURE 2

## GEOGRAPHICAL DISTRIBUTION OF HEMOPHILIA CENTERS ACROSS ITALY (17)



During this phase, a treatment plan must be either drawn up or updated, in order to ensure continuity in the supply of appropriate amounts of drug, administered by the most appropriate method. The check-up examination also provides an ideal context for receiving information on new therapies and discoveries in the field of hemophilia, where patients can ask freely clarification or further details on the subject.

In addition to the above, centers should also be capable of offering:

- Round-the-clock availability in case of a hemorrhagic emergency;
- Hospitalization, in case further investigations and treatment are required in an in-patient regime;
- Check-up visits for patients affected by liver disorders and/or by HIV infection, in order to monitor related complications;
- Psychological counseling for pediatric patients;
- Home-care training;
- Counseling and genetic diagnosis on the

disease's mode of transmission, genetic diagnosis tests and prenatal diagnosis (16).

In actual practice, assistance to patients affected by congenital bleeding diseases varies greatly from region to region (17).

While most regions have not yet started an institutional, structured process for the creation of a territorial network which ensures appropriate care along the entire diagnosis, therapy and assistance cycle, some regions have already organized their services according to a network model. For example, the Emilia Romagna region has organized a 'hub and spoke' model, which consists of a single Regional Coordination Centre (hosted by the Hospital and University Unit of Parma - *Azienda Ospedaliero-Universitaria*, in short AOU), with seven in-hospital Hemophilia Centers (in the AOU of Bologna, Ferrara, Modena, the Hospital Unit of Reggio Emilia, and the Healthcare Units of Piacenza, Ravenna and Cesena), and, finally, a Regional Registry managed by the Regional Coordination Centre (18).

The hub-and-spoke model developed in Emilia Romagna is based on a dynamic system of interconnections among several Centers treating patients in different stages of their diagnosis, therapy and assistance cycle, according to different levels complexity of care. The main functions of the Spoke Centers are:

- Global assistance in all stages of the disease;
- 24-hour availability;
- Laboratory diagnostics (first and second level);
- First-level genetic counseling;
- Organization of self-infusion courses;
- Promotion of programs for prevention, information and training.

In addition to the functions provided by Spoke Centers, the main functions of Hub Centers are:

- coordinating the network and the 24-hour over-the-phone assistance service;
- determining diagnosis, therapy and assistance cycles and treatment protocols;
- coordinating competences encompassing multiple specialized skills;
- Second-level molecular diagnosis and genetic counseling;
- coordinating self-infusion courses;
- organizing training courses;
- establishing and managing the Regional Disease Registry.

The strength of the model lies in its precise definition, which, by its very nature, enables monitoring and checking of performance and ensures high-level and consistent qualitative treatment standards all over the Region, thus promoting the optimization of resources.

The model also enables the opposite needs to be met, of providing services as extensively as possible through providers located as close as possible to the users, against a background of just a small number of highly-qualified centers in which to concentrate highly-professional specialized competencies. Within this model, the Regional Registry of Congenital Bleeding Disorders plays an important role in implementing epidemiological surveillance and monitoring the quality of the assistance and care being delivered.

The Project for implementation of this Registry was presented in September 2002 by the Parma Centre; it was approved and financed by the Emilia Romagna Region in the same year and was outstanding in terms of innovation.

Its main goals are:

- To provide regional epidemiological data;

- To monitor the disease and its complications;
- To highlight trend in pharmaceutical and healthcare costs;
- To monitor treatment regimes, hospitalizations and surgical interventions;
- To gather data on quality of life and social aspects;
- To ensure the quality of data collected in Centers and, therefore, the delivery of assistance.

Patient data is entered in the computerized medical records of the various Hemophilia Centers once informed consent has been obtained in writing. Data is processed in compliance with Italian privacy laws, ensuring absolute privacy, confidentiality and security of data. The Centre is also responsible for the quality and accuracy of data collected, a part of which – that selected for the Registry – is sent to the Regional Coordination Center in Parma once every six months. Once the data has been entered into the Parma database, it is published on a dedicated website ([www.registroemofiliarer.it](http://www.registroemofiliarer.it)), which was developed in 2003 by the AOU of Parma. The site is divided into two areas: public and restricted (19).

For these reasons, the hub-and-spoke model of the Emilia Romagna Region has set an example of best practice to be exported to other regions. Indeed, alongside well-structured, appropriately sized Centers providing comprehensive care in full compliance with the “European Principles of Hemophilia Care” (2), in other Regions smaller structures can also be found, which are not properly organized and often without official recognition; such centers manage to provide partial, limited assistance.

The Lazio Region has recently begun to reorganize itself according to the Hub & Spoke model; the hub is intended be the Hemophilia Centre at the Policlinico Umberto I in Rome, and seven satellite centers across the regional territory have been officially recognized (20).

A similar process has been implemented by the Apulia Region, where, the Regional Decree of August 4<sup>th</sup>, 2010, recognized the Hemophilia Centre of the Complex Operational Unit of the Immune Hematology and Transfusion Medicine of the Hospital Unit of the Bari Policlinico Consorziiale as its hub. The same Decree recognized eight Spoke Centers (21).

Assistance to patients affected by hemophilia cannot be considered to be evenly provided

across Italy's national territory, but also within the same region the service supplied may vary from one individual province to another.

Such considerations stress the need for the implementation of targeted measures aimed at continuously improvement of quality, especially with regard to technological equipment and professional skills.

In this regard, in 2006 AICE started a process aimed at implementing a professional certification system for Centers operating in the national territory: the "Improve AICE" project was aimed at achieving high-level professional standards and at adopting policies based on continuous improvement and best practices, to be certified through a transparent and strict assessment process.

The goals of the "Improve AICE" Project are:

- "To promote the provision of high-quality assistance services, in order to ensure that patients receive appropriate, constantly updated and consistent care in terms of quality and methodology, all over the national territory.
- To draw up a reference model based on the principles of clinical management, in order to reduce uncertainty and individual experience components which are intrinsic in healthcare activities and to support the adoption of objective criteria for assessing activities and objectives achieved.
- To implement a dynamic system based on best practice, capable of evolving in response to the context of reference and to technical and scientific progress, in order to guide Centers toward continuous improvement of their performance quality and respective outcomes.
- To foster comparison between Centers in terms of quality, to be understood in terms of their overall management organization, clinical and diagnostic activity quality and patient-centered approach.
- To plan a system of standards and an assessment model capable of being integrated with other reference models (institutional certification, ISO 9 000 certification, etc.).
- To activate a professionally qualified, objective, independent and systematic peer assessment process, which is compliant with defined standards and to facilitate the achievement of expected results, also involving also the Patients' representatives" (22).

The Project, developed during 2007-2008, included:

- The determination of strategic guidelines for development of the Professional Certification Model by AICE;
- The drafting of an AICE Standards Handbook on Hemophilia and rare bleeding diseases, both inherited and acquired;
- The definition of assessment criteria in the framework of the AICE Certification Program;
- The designing of AICE Certification Procedures.

Furthermore, during the two-year period 2009-2010, the following activities were developed:

- Testing of the AICE Professional Certification Model (auditing activities carried out by 4 especially trained assessors at the 6 pilot centers in Cesena, Bologna, Sassari, Palermo and 2 centers in Turin, previously selected according to their geographical distribution, number of patients with hemophilia being treated, laboratory equipment available and care provided to pediatric patients);
- Sharing of the AICE Standards Handbook among all Centers;
- Review of the Model's elements;
- Launching of the AICE Certification Program (22).

The Project went fully online in 2009 and the Certification procedure for applicant Centers is currently under way.

Furthermore, on a dedicated site ([www.improveaice.it](http://www.improveaice.it)), there is a section where Center directors assess services provided by their own structure against AICE standards. Indeed, self-assessment may provide:

- A good opportunity for debate and professional growth of the Centre's staff;
- The opportunity to determine strengths and weaknesses of individual structures;
- A stimulus to enhance guarantees delivered to the patients and to continuously improve performance (22).

### **PROPHYLAXIS AND HOMECARE FOR PATIENTS AFFECTED BY HEMOPHILIA: POSSIBLE OBSTACLES AND STRATEGIES FOR DEALING WITH THEM**

The section on treatment (see Chapter 2) clearly illustrated the clinical value of the

prophylaxis regime in treatment of hemophilia. In 1994, the WHO and the WFH recommended primary prophylaxis in children affected by severe hemophilia from their first years of life for an indefinite period as prophylaxis is deemed to be the ideal treatment strategy to prevent bleeding and its sequelae (23, 24).

Secondary prophylaxis, started in adolescent and adult age, had also shown greater benefits than on-demand treatment (25). A study carried out by Tagliaferri et al. in 2008, found that secondary prophylaxis in these patients led to a significant reduction in the annual number of bleeding episodes and of lost days of work or school and contributed to an improvement in joint function (26).

Prophylaxis consists of administering clotting factor VIII to prevent bleeding before the onset of bleeding episodes. This treatment mode, requiring drug administration several times a week in a continuous and regular way, can also be conducted at home, in the framework of a nurse assistance program (home nursing) (27, 28). When patients with hemophilia strictly comply with treatment prescription by the Hemophilia Centers, (and home nursing will certainly promote compliance), prophylaxis can ensure them a completely normal life (29). Indeed, regular home infusion of clotting factors:

- can help avoid episodes of acute bleeding which may endanger the patient's life;
- can reduce the number of complications arising after joint bleeding. When recurrent, joint bleeding may lead to degeneration of the joints themselves;
- can reduce the number of days of hospitalization and lost days at work or school, allowing the patient to take part regularly in social and productive life.

However, although prophylaxis is increasingly recommended, there are several conditions which may lead to its suspension and even to treatment rejection, such as:

- Difficult venous access;
- Distance from the reference Hemophilia Centre;
- Low level of compliance (by patient and/or family);
- Socio-economic level.

A relevant problem in hemophilia treatment, especially with very young children treated with primary prophylaxis (with intravenous drug administration every 3-4 days) is the type of venous access to adopt: injection in a

peripheral vein, central venous catheter (CVC) or arterial-venous fistula (30).

Injections allow drug infusion directly in a peripheral vein, usually on the arm: this mode of administration entails a low risk of infections, even if the injection site needs to be changed frequently to avoid damage to veins (31). In the case of home care treatment, when nursing staff is not available, it is necessary to have expertise in the technique, otherwise there is a risk of having to inject into veins several times for a single infusion, with consequences, including psychological ones, on the child.

CVC is a small tube made out of biocompatible material which allows intravenous infusion, either intermittent or continuous. It must be inserted in a central vein, so that the tip is placed in the lower third of the superior vena cava. Compared to peripheral venous access, CVC ensures a stable venous access and, when properly managed, a low risk of infectious and thrombotic complications (32). The tube must be inserted by a doctor or a specialized nurse in an adequate setting (not necessarily an operating theater: a dedicated out-patient room is sufficient). When well tolerated, such a device may prove less traumatic, because the child learns not to be afraid of injections. Furthermore, in order to use and manage CVC, it is not necessary to master complicated skills or procedures; all you need is to comply with aseptic injection procedures and carry out the required washings (33).

The arterial-venous fistula is performed by connecting a vein with an artery, so that the vein increases in size and can easily be detected for injection. This method makes infusion easier than in the traditional peripheral vein, especially in those children whose venous access is difficult to detect (30).

There is probably no such thing as a single technique of choice, because the same method can be experienced in different ways, according to the parents' previous experiences. Therefore, treatment can be selected after having consulted a specialist, talked to other parents who are already treating their children with prophylaxis and accessing information personally. Furthermore, as previously mentioned, a significant contribution to overcoming practical difficulties involved in intravenous drug injection can come from home nursing.

As stated in previous sections, patients affected by hemophilia need to refer to their Hemophilia Centre frequently and continuously for diagnostic and follow-up activities, periodical medical examinations and laboratory check-ups, according to the severity of the underlying disease and of concomitant disorders (see Chapters 1, 2 and 3). However, for many patients, the reference Centers are located far away from their homes and this forces them to endure long and frequent journeys. Therefore, it is necessary to implement an organization plan for assistance through a network of structures which ensure a pervasive response to patient needs (the Hub & Spoke model was described in detail previously in this chapter), with equal access opportunities, regardless of the patient's address.

With regard to lack of compliance with prophylaxis treatment, the findings of a study carried out by Hacker et al. in 2001 show that families who chose not to start prophylaxis did so for a variety of reasons, both objective in nature (mainly connected the high frequency of administration, implying an intense organizational and psychological commitment for the whole family) and individual in nature (such as concerns over the drugs' contraindications and the tendency to make use of invasive procedures only in emergency situations (34).

A more recent study, carried out by Beeton et al. in 2007, confirmed that compliance with prophylaxis treatment is the consequence of processes within the family's organization, and of fears and concerns over the child's future and with the responsibility that the parents feel towards managing the treatment by themselves (35).

The choice of prophylaxis can be also influenced by the opinion of the medical staff treating the child, who may have different views on the severity or medical phenomenology of the disease as a discriminating element leading toward choosing one mode of therapy over another. Indeed, treatment indications by doctors are influenced by the body of scientific knowledge they take as their reference, by personal assessment of the risk/benefit ratio within the range of possible measures, and by the general policies implemented by the Service provider they work for.

Finally, this choice may also be influenced by the socio-economic level of the patient and/or his/her parents, the nature of doctor/patient interactions and the degree of trust in the doctor (35).

Home nursing is therefore a treatment

mode of choice and not simply an alternative to hospitalization. However, it must comply with the principles of complexity and global extent of treatment: the patient receiving treatment must enjoy the same level of protection as in a hospital environment (36).

Being of central importance in the education to self-management of the disease, home nursing should, therefore, provide all the conceptual, methodological and functional ingredients required. These should include:

- Infusion of anti-hemophilic factor during prophylaxis, in case of emergency and in case of immune tolerance;
- Control of venous accesses;
- Global care of the patient, encompassing, among other things, psychological and social aspects of the disease, in order to ensure better quality of life (37).

Home nursing should therefore be based on a team of specialized nurses who received previous targeted training, and who are able to educate and monitor patients and their families in the process of infusion/self-infusion until they acquire complete independence in managing the disease.

In fact, no legislative framework exists at the national level regarding home nursing and only some regions have issued a Regional Law (Table 1) identifying structures, assigning competences, coordinating modes of family/patient training and identifying the patient's duties (38-47).

Furthermore, home nursing, which is one of the main priorities of all Regional Healthcare Plans, would prove beneficial also from the financial point of view, as it helps reduce hospitalization costs, thus helping to effect the required reductions in healthcare expenditure, since it replaces short or inappropriate hospitalizations.

In recognizing the value of out-of-hospital treatment that is managed mainly on a home-care basis, Baxter has provided patients affected by Hemophilia and National Healthcare Systems with a package of free homecare services aimed at implementing assistance. The package combines treatment requirements with the need to improve the patient's quality of life and facilitate access to services (48). This homecare service is organized in the following way (Figure 3):

- Home assistance to patients affected by hemophilia - Home Clinical Assistance (HCA);
- Home physiotherapy service - Home

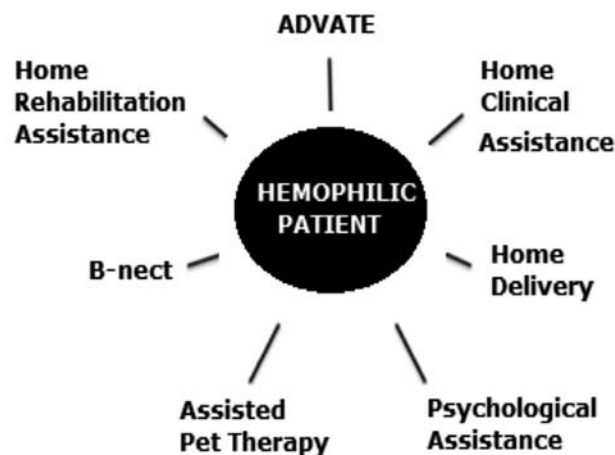
TABLE 1

SUMMARY OF ITALIAN REGIONAL LAWS ON HOME CARE OF PATIENTS AFFECTED BY HEMOPHILIA IN ITALIAN REGIONS

REGION	REGIONAL LAW
Calabria	May 30th, 1986, No.22
Emilia-Romagna	April 20th, 1977, No.17
Lazio	September 28th, 1979, No.80
Liguria	January 7th, 1980, No.5
Lombardia	June 12th, 1975, No.88
Marche	September 15th, 2008, No.197
Piemonte	May 16th, 1979, No.26
Sardegna	May 8th, 1984, No.19
Toscana	May 24th, 1980, No.62
Veneto	July 31st, 1984, No.37

FIGURE 3

BAXTER'S APPROACH TO PATIENTS AFFECTED BY HEMOPHILIA



Rehabilitation Assistance (HRA);

- Home Delivery Service of drugs;
- Multimedia platform “B-nect/mobile patient care”;
- Pet therapy;
- Psychological counseling services – Psychological Assistance.

The HCA service provides free home nursing assistance. It offers hemophiliacs all the above-mentioned benefits of home nursing. It is provided by a team of specialized, purpose-trained nurses and is aimed at training the patient or his/her relatives in carrying out self-infusion

at home. In this way, the HCA service supports the Hemophilia Centre in helping the patient become self-sufficient in the management of their treatment routine, reducing obstacles to the adoption of prophylaxis and, therefore, improving the patient quality of life and their inclusion in social and family life (49).

Alongside home nursing assistance, the HRA home assistance program of physiotherapy promotes compliance with the necessary rehabilitation programs at the patient's house, both in case of post-surgery rehabilitation and in daily prevention of joint degeneration. By means of constant exercise, patients with

hemophilia improve their muscle tone, thus reducing the risk of damage to target joints. The project includes exercises to do at home, thanks to the Wii Fit board, a device in the Nintendo console, so that physical therapy becomes a time of relaxation, especially for younger patients, who can approach activities in a playful way that are at the same time therapeutic exercises (50).

Furthermore, the Home Delivery Service project includes home delivery of drugs, so that patients residing in areas remote from Hemophilia Centers do not have to undertake long journeys from the Hemophilia Centers.

This also removes all the problems related to drug storage and distribution, ensuring patients the practical solution: having all the solutions and accessories available in their own homes (51).

B-nect is an innovative multimedia platform which enables the shortening of distances between hemophilia stakeholders, and makes treatment management even more effective. Thanks to Cisco's Web EX technology, this service includes supply of an IT device, especially designed and installed on a mobile phone device such as a smartphone, enabling patients to:

- keep in touch with their treatment center;
- manage their own therapy by writing their infusion journals;
- take part in on-line informative sessions organized by their center;
- gain access to important information on their therapy.

B-Nect is also an important instrument for clinicians, since it allows them to:

- monitor patient compliance to the recommended treatment regime;
- issue and receive news from patients about treatment;
- organize and lead sessions aimed at updating and/or carrying out in-depth analysis with patients.

Furthermore, B-nect is directly linked to the Italian Registry of Congenital Coagulation Disorders, Emoweb, thus making the management of the Registry itself even simpler and automated and reducing the burden of work on Centers (52).

As a consequence, by overcoming logistics-related obstacles, such a device allows distances between the doctor and the patient to be

shortened, and helps patients themselves to increase their social interaction and quality of life (QoL) (52). Due to these potential benefits, Baxter Italia, with B-nect Mobile Patient Care, was awarded Cisco's Innovation Award 2011 in the category: Most Society Impacting Network category, as the "company which makes best use of Net potential to the benefit of society" (53). The jury of the award adjudged B-nect to be the best project "because it improves the doctor-patient relationship, creates a community and shortens the distance between patients affected by hemophilia in Italy" (54).

Baxter has devoted a special focus to the psychological aspects of patients affected by hemophilia.

With the aim of promoting social integration and improving patients' QoL, Baxter funds psychological and physical rehabilitation programs based on equine-therapy. Indeed, evidence exists that assisted pet therapy can be useful for patients affected by chronic diseases, who may overcome psychological limitations imposed by the individual's condition and improve social interaction (55).

In this regard, Baxter has also established a psychological assistance service for patients affected by Hemophilia And their families (psychological assistance). This service originates in the awareness that the quality of life of children with hemophilia is closely bound to that of their family. Targeted psychological support, in line with the directions given by the doctor at the Hemophilia Center, will certainly be of real help in achieving that state of well-being so fundamental in patients affected by chronic diseases such as hemophilia.

All services promoted by Baxter described so far are examples of cooperation between the National Health Services and a pharmaceutical company, an example of synergy aimed at serving the patients' interests, at making better use of and reducing healthcare expenditure, and at achieving a fair 'sustainable' profit by the company itself. In other words, it is in line with the needs of the society where the company operates collaboration with local-level structures. Such synergy should be established between all stakeholders in order to provide a global assistance scheme which has the patient at its center.

Moreover, as a first in the field of hemophilia treatment, Baxter has introduced a risk-sharing policy, imported from other treatment sectors, which provides for the co-participation in the expenditure of the National Healthcare System



in the case of implementation of immune tolerance programs using Advate.

This arises from a context in which it is necessary to strike a balance between innovation and financial compatibility, and also from the findings of the post-marketing surveillance study on Advate: PASS (Post authorization safety surveillance) (56) (see Chapter 4). This study showed a low incidence of de novo inhibitors (0.29%; CI 95% = 0.01% - 1,59%) in PTPs (Previously Treated Patients) with FVIII levels  $\leq 2\%$ , and no history of inhibitors, treated with Advate. This result was demonstrated on a study population deemed to be the most appropriate for assessing the immunogenicity of the product, as established by the guidelines of the EMA and FDA (see Chapters 2, 3 and 4). The finding led the company to adopt an innovative private-public partnership model. Indeed, Baxter intends to support the Italian National Healthcare System by guaranteeing to patients the implementation of immune tolerance induction (ITI) programs using Advate, thus achieving significant savings on treatment costs. The model provides for a 50% discount on the ex-factory price of Advate when it is used for immune tolerance in patients who have been treated with this drug and who have developed an inhibitor after 50 cumulative days of product exposure (PTPs). The same model also provides for a 5% discount on the ex-factory price of Advate in cases of immune tolerance in patients treated with this drug, whose inhibitor diagnosis was made before the 50 cumulative days of product exposure (Previously Untreated Patients and Minimally Treated Patients respectively).

These initiatives are of considerable interest, especially against the background of future scenarios, where patients affected by Hemophilia are likely to develop at least one concomitant disorder (cardio-vascular, tumor, metabolism disorders), seriously impacting on their clinical management and increasing the burden on Hemophilia Centers (57). In recent years, these patients have shown an increase in the incidence of hypertension and diabetes in comparison to the general population (58), probably due to their life-style (lack of exercise, smoking, eating habits) and to the use of corticosteroid drugs for the treatment of chronic joint disease. An increase is also being observed in the prevalence of tumors, probably related to the increase in the average age of the community of patients with hemophilia (59).

This poses several problems related, e.g., to assistance management, invasive measures for differential diagnosis and the collateral effects of chemotherapy. A response to this emerging situation might consist in implementing a complex assistance model which, while taking into account available structural and financial resources:

- develops local multidisciplinary assistance programs;
- includes an area for home care;
- promotes optimization of adopted measures, also regarding prescription accuracy;
- develops training and information programs for the patient and his/her family.

Associations of people affected by the disease have for some time now played a vital role in making up for the lack of response by the social and healthcare assistance system. These associations, which include a wide range of organizations sharing the goal of informing and supporting patients according to their assistance-related needs, have helped, supported and above all 'lent a voice' to the needs of patients and their families.

These associations are the critical conscience of civil society: they work in order to shed light on and tackle the difficulties that patients and their families have to face every day, thus giving the world of medical research fresh impetus to seek new solutions for the diagnosis and treatment of rare diseases. The associations also keep their members and the general population informed on such issues. Such civil commitment is extremely important and its support should be accessible to patients, doctors, citizens and institutions alike.

FEDEMO, an ONLUS (Non-Profit Organization for Social Purposes) is very active in the specific field of protection of the rights of patients with hemophilia. FEDEMO was created in 1996 and it took up the cultural heritage and commitment of the Foundation for Hemophilia, founded in 1969.

Among the main aims of the Federation, as described in the Association's Charter are:

- "to be active in tackling medical and social issues facing patients with hemophilia in Italy and to coordinate, support and represent the Associations of patients affected by Hemophilia And other

coagulation diseases before national and international institutions;

- to inform, educate, stimulate and coordinate all activities aimed at improving clinical and welfare assistance to patients with hemophilia in Italy and to foster scientific research in the field of coagulation disorders and genetic treatment;
- to stimulate and support Hemophilia Centers in every Region and to help create services for bleeding emergencies in close proximity to the places where patients affected by hemophilia reside;
- to carry out effective cooperation with AICE, thereby fostering promotion and organization of the National Congress on clinical and social issues related to hemophilia;
- to represent and support associations and individuals before administrative and judicial authorities in obtaining fair and equitable damage compensation for viral infections caused by plasma-derived drugs as well as before medical assistance authorities in obtaining the most modern prevention measures, emergency and home-care treatments available in Europe” (60).

The Federation carries out the following activities:

- “It represents patients with Hemophilia At the highest institutional levels;
- It takes part in the works of technical bodies of the Healthcare Ministry, such as the National Commission on Transfusion Services and the National Consultative Body on AIDS;
- It helped design and implement projects in the framework of the national campaign for information on and prevention of AIDS;
- It represents Italy within the WFH, an association of patients and scientists certified by the WHO;
- It helped make drugs obtained through recombinant DNA technology available in Italy.
- It helped improve laws regarding compensation for biological damage caused by transfusions and participates in the Healthcare Ministry Permanent Committee on Law 210/92;
- It disseminates an information bulletin throughout the national territory;
- It promotes counseling and information activities to patients through A.C.E. - the Association of Patients Affected by Hemophilia And other Coagulation Disorders of Milan” (60).

Thirty-one first and second level local Associations are currently members of the Federation, between them representing approximately 7 000 Italian patients affected by coagulation disorders (61).

In conclusion, the network of relations between doctors, researchers, institutions and patients, which is soon to be enriched by the federated effort of the Regions and their varied range of healthcare competencies, also includes associations. Especially in the case of rare diseases, these associations play a vital role both in patients’ everyday lives and in that of the centers for treatment and research.

## PATIENTS’ QUALITY OF LIFE

Here the term ‘quality’ refers to a series of factors which bear - both directly and indirectly - on multiple aspects of life. Reference is made to Health Related Quality of Life HR-QoL, i.e. the state of health associated with QoL (62). HR-QoL encompasses the physical, emotional, mental, social and behavioral components of well-being and of functionality as perceived by patients and/or assessors. It is therefore a fundamental variable to take into considered when choosing the most appropriate treatment to be prescribed to patients with hemophilia (63).

In the case of complex disorders such as hemophilia, the multi-dimensional assessment of patient QoL becomes a core element in the analysis of how and to what extent treatments influence the improvement of QoL.

Over recent years, several HR-QoL assessment models have been proposed; currently, general questionnaires are available, which refer to all types of patient case reports, aimed at analyzing, in a multidisciplinary way, the several aspects impacting on QoL. According to the WHO, the most commonly used questionnaires are: the 36-item Medical Outcome Study (MOS), the Short-Form Health Survey (SF- 36), the EuroQoL-5 Dimensions (EQ-5D) (64, 65) and the Child Health Questionnaire (66, 67). As the available scientific sources confirm, most studies rely on the SF-36 (68, 69). In addition to these, ad hoc questionnaires have been introduced for hemophilia; compared to the general questionnaires, these are more specific and allow easier comparison, providing a detailed picture of specific symptoms and disabilities associated with the disorder under study. If, on the one hand, general instruments

TABLE 2

## HR-QOL QUESTIONNAIRES SPECIFICALLY ON HEMOPHILIA DEVELOPED AT THE NATIONAL LEVEL

ACRONYM	NAME	AGE GROUP	LIST OF REFERENCES	COUNTRY OF ORIGIN
CHO-KLAT	Canadian Hemophilia Outcomes-Kid's Life Assessment Tool	Pediatric	Young et al. 2004	Canada
Not available	Quality of life for young patients	Pediatric	Manco-Johnson et al. 2004	USA
Hemophilia-QOL	Disease-specific QOL questionnaire to adults living with hemophilia	Adult	Arranz et al. 2004	Spain
Hem-A-QOL	Hemophilia QOL questionnaire for adults	Adult	v. Mackensen et al. 2004	Italy

TABLE 3

## HR-QOL QUESTIONNAIRES SPECIFICALLY ON HEMOPHILIA DEVELOPED AT THE INTERNATIONAL LEVEL

ACRONYM	NAME	AGE GROUP	LIST OF REFERENCES	COUNTRY OF ORIGIN
HEMO-QOL	Hemophilia Quality Of Questionnaire	Pediatric	v. Mackensen et al. 2004	Europe
Medtap	Not available	Adult	Flood et al. 2003	USA, Canada, Germany, Spain
Hemolatin- QOL	Disease-specific quality-of-life questionnaire to adults living with hemophilia	Adult	Remor et al. 2004	South America

Modified from von Mackensen et al. 2010 (62)

allow the QoL of patients with hemophilia to be compared with the quality of life of those affected by other diseases, or with that of the general population, specific assessment instruments, on the other hand, being much more precise and specifically designed for this disease, provide more detailed information and allow more precise measurement of the patients' state of health (70). Alongside ad hoc measurement scales, other instruments have been developed and approved at the national and international level: Hemo QoL, and the Canadian Hemophilia Outcomes – Kids Life Assessment Tool (CHO-KLAT), aimed at assessing quality of life in children with hemophilia; Hemophilia-QoL and Hemolatin-QoL, for the assessment of HR-QoL in adults (Tables 2 and 3) (62).

Several studies carried out in recent decades, have aimed at assessing the health status of hemophiliacs and have shown that hemophilia

has a significant impact on the patients' QoL, especially with regard to its associated complications in terms of pain, joint disease and disabilities, in addition to impacts on the emotional and psychological status of affected individuals (62, 70-73) (see Chapters 1-3).

Tables 4 and 5 report several variables - related to both to the disease and its treatment - and to those clinical and psychological burdens which mostly impact the patients' QoL (62).

In affecting patients with hemophilia both frequently and unexpectedly, bleeding causes significant problems, since it prevents patients from planning their future activities and impacts on their health status. CVC, which is employed for periodical infusions, exposes patients to the risk of contracting bacterial infections and sepsis. These conditions may, in turn, trigger a worsening of patients' QoL. Also hemophilia-related joint disease contributes to the deterioration of the health status, and,

TABLE 4

DISEASE AND TREATMENT-RELATED ISSUES	
DISEASE-RELATED ISSUES	TREATMENT-RELATED ISSUES
Spontaneous and post-trauma bleeding	Frequent intravenous injections
Life-threatening bleedings	Central Venous Catheter
Common bleedings	Catheter-related infections
Acute pain	Catheter-related thrombosis
Non-predictable bleeding episodes	Allergic reactions
Hemophilic joint disease	Hematogenous viral infections
Chronic pain	Inhibitor development
Disability	Collateral effects related to the use of NSAIDs
Mortality	

Modified from von Mackensen et al. 2010 (62)

TABLE 5

CLINICAL AND PSYCHOLOGICAL BURDEN	
CLINICAL BURDEN	PSYCHOLOGICAL BURDEN
Pre-natal diagnosis	Issues (work, education, family etc.)
Health state	Coping <sup>1</sup>
Complications (inhibitors, disability)	Anxiety
Treatment (regime, venous access)	Depression
Collateral effects (infections, allergic reactions)	Stigmatization and discrimination

Modified from von Mackensen et al. 2010 (62)

therefore, of the QoL of these patients.

The development of inhibitors - antibodies that are able to interfere, totally or partially, with the activity of clotting factors, severely complicates the clinical profile of hemophilia, also affecting the management of the bleeding episode and rendering prophylactic treatment impossible (74, 75). Anxiety, depression, social problems, discrimination by peers and so-called 'coping'<sup>1</sup> syndromes, are all psychological factors which may undermine the general state of health of patients with hemophilia (Table 5).

As it was amply discussed in the Chapter devoted to treatment (see Chapter 2), the introduction of prophylaxis and the availability of third-generation clotting factors has provided

patients with the opportunity to improve their health status profile and QoL (71, 76).

With regard to research into the HR-QoL of patients with hemophilia, significant evidence was provided by the PASS (Post-Authorization Safety Surveillance) study on Advate (56), carried out in 123 centers (92 in Europe and 31 in the United States) on 205 patients being treated with prophylaxis or on-demand treatment. This study provided for the administration of SF-36v2 and showed that hemophilia impacts more on the physical component than on the mental sphere (Table 6).

In the framework of the PASS Study, the HR-QoL of patients with hemophilia was compared both with the HR-QoL of the general

<sup>1</sup> The term "Coping" (also "active management", "effective response", "problem-solving skill") indicates a set of mental and behavioral strategies implemented in order to deal with a specific situation.

TABLE 6

## QUALITY OF LIFE OF PATIENTS WITH HEMOPHILIA VS. GENERAL POPULATION, HEALTHY POPULATION AND PATIENTS AFFECTED BY OTHER CHRONIC DISEASES

	HEMOPHILIA A (N=205)		HEALTHY POPULATION (N=2 079)		GENERAL POPULATION (USA) (N=7 069)		BACKACHE (N=2 648)		RHEUMATOID ARTHRITIS (N=514)		DIABETES (N=545)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
PF	42.9	0.81	53.4‡	0.25	50.3‡	0.23	47.5‡	0.40	45.6	1.80	43.5	2.27
RP	44.5	0.75	53.9‡	0.23	50.5‡	0.24	47.1	0.43	44.6	2.06	42.6	2.30
BP	44.4	0.72	54.3‡	0.30	49.8‡	0.24	44.7	0.37	41.5	1.48	41.1	2.01
GH	41.9	0.81	54.3‡	0.27	49.4‡	0.24	45.6‡	0.42	41.0	1.67	38.4	2.08
VT	51.0	0.58	51.5	0.32	47.8\$	0.24	44.3\$	0.40	43.3\$	1.60	43.0\$	2.10
SF	48.3	0.73	52.6‡	0.25	40.0	0.25	45.7 t	0.45	44.4 t	1.84	42.4 t	2.35
RE	46.5	0.79	52.5‡	0.23	49.3‡	0.25	46.8	0.46	44.7	1.99	45.1	2.65
MH	48.5	0.71	51.1‡	0.29	47.7	0.24	44.5\$	0.42	42.5 t	1.72	42.9	2.16
PCS	42.3	0.77	54.5‡	0.24	50.7‡	0.23	46.9‡	0.40	43.6	1.89	41.3 t	2.18
MCS	50.5	0.75	51.5	0.27	47.7\$	0.24	45.0\$	0.44	43.0\$	1.99	43.8 t	2.32

PF= physical functioning; RP= role limitations due to physical health (role-physical); BP= bodily pain; GH= general health; VT=vitality SF= social functioning; RE= role limitations due to emotional health (role-emotional); MH= mental health PCS= Physical Composite Score; MCS= Mental Composite Score.

\*Comparison group > Hemophilia group,  $P < 0.05$   
 † Hemophilia group > Comparison group,  $P < 0.05$   
 ‡Comparison group > Hemophilia group,  $P < 0.001$   
 \$Hemophilia group > Comparison group,  $P < 0.001$

Modified from Klamroth et al. 2011 (56)

population and with that of patients affected by other chronic conditions (backache, rheumatoid arthritis and diabetes).

Patients affected by hemophilia scored significantly worse than the healthy population on all assessment scales, except the VT (Vitality) and MCS (Mental Composite Score).

The findings of the comparison between patients with Hemophilia And patients affected by other conditions have shown that the disease has a physical impact which is equivalent to that of diabetes and rheumatoid arthritis and higher than the impact of backache. Regarding backache, the scores of patients with Hemophilia Are significantly lower, both from the statistical and the clinical points of view (difference > 3 scores) in 3 out of 4 physical scales: Physical functioning (PF); Role limitations attributed to physical health (RP); General health (GH) and the PCS (Physical Composite Score). As far as mental health is concerned, the scores of patients with Hemophilia Are generally higher

than those of patients affected by other chronic disorders, especially against the VT scale, with clinically significant differences.

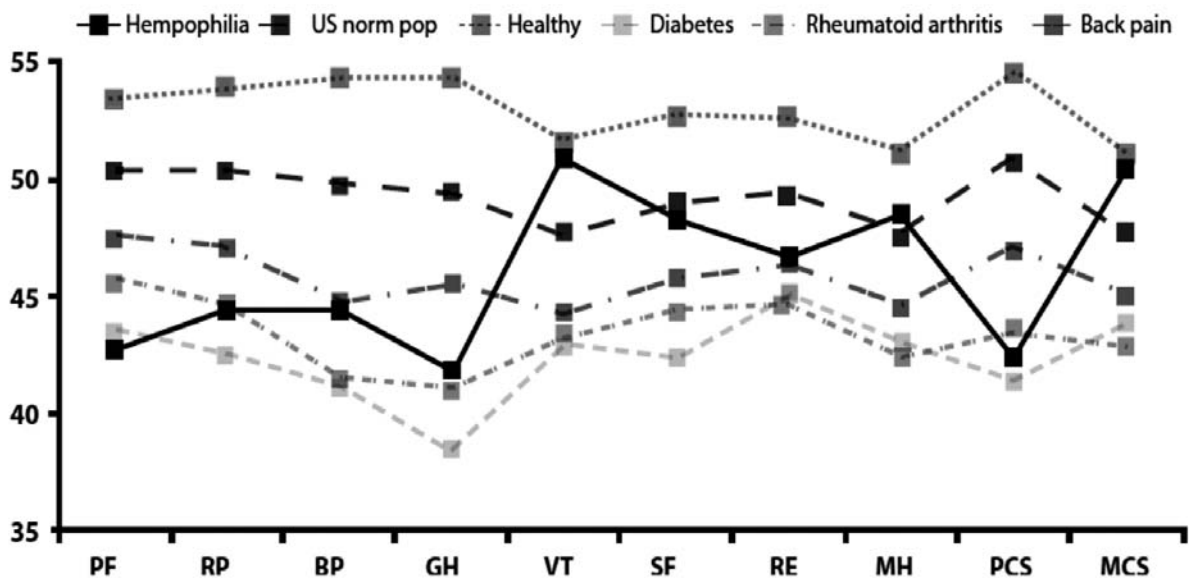
These data may derive from the fact that, since hemophilia is a congenital disease, patients learn to live with this condition from their early years, suffering from the physical limitations associated with the disease rather than from disease-related psychological distress.

The findings of the Advate PASS study once again confirm the importance of prophylaxis: unlike on-demand treatment, it can prevent complications causing disability and events imposing limitations on the patient's social life starting from their earliest years of life. If started in the first years of life (77), prophylaxis can prevent the onset of hemarthrosis and reduce the number of bleedings, thereby preventing permanent damage to joints and the associated chronic pain (Figure 4).

Further studies aimed at investigating these results in greater depth, especially through the

FIGURE 4

SF36V2 SCORES OF PATIENTS WITH HEMOPHILIA A COMPARED TO THOSE OF THE GENERAL POPULATION, BOTH HEALTHY AND AFFECTED BY CHRONIC DISEASES



PF= physical functioning; RP= role limitations due to physical health (role-physical); BP= bodily pain; GH= general health; VT= vitality SF= social functioning; RE= role limitations due to emotional health (role-emotional); MH= mental health PCS= Physical Composite Score; MCS= Mental Composite Score.

Modified from Klamroth et al. 2011 (56)

use of specific questionnaires, may provide further evidence about this issue. In this regard, the AHEAD study (*Advate in Haemophilia A outcome Database*), currently underway, aims to assess the quality of life of patients affected by hemophilia using the Haem-A-QoL, Haemo-QoL, SF10 and SF12-second version measuring scales (78).

## CONCLUSION

The treatment of patients with hemophilia requires a multidisciplinary healthcare approach, highly complex care and a high level of resource consumption. For this reason, knowledge of epidemiological data and treatment-related data regarding the various forms of coagulation disorders gathered from each region and on a national scale are vital aspects of care-provision planning and care programs. Regional and national registries therefore offer a vital instrument for national healthcare systems and are of primary importance when undertaking action aimed at improving the management of congenital coagulation diseases.

Due to the degree of specialization in the

skills required, it is necessary to ensure that centers for hemophilia diagnosis and treatment are organized in a well-articulated way. They have to ensure provision of a wide range of services, such as round-the-clock availability, hospitalization, check-ups, psychological advice, home-care training, counseling and genetic diagnosis.

The care actually provided to hemophiliacs presents inconsistencies not only on the national scale, but also within individual regions: the situation often varies from one province to another. The need therefore emerges for targeted measures aimed at constantly achieving and improving the quality of care provision, especially with reference to technological equipment and professional figures working in the centers.

Prophylaxis, unlike on-demand treatment, can lead to the prevention of complications causing disability and the amelioration of events imposing limitations on the patient's social life, starting from the patient's earliest years. Prophylaxis provides for drug administration several times a week, in a continuous and regular way; the drug can be administered

at home within the framework of a home-care program. When accompanied by precise and meticulous compliance with the treatment prescribed by the reference centers, this treatment mode may guarantee to hemophiliacs the ability to lead a completely normal life. However, taking into consideration possible obstacles to effective implementation, home nursing care should be implemented by a team of specialized nurses, who have previously undergone targeted training and who are able to educate and monitor patients and their families regarding infusion/self-infusion practice until they are completely independent in managing the disease.

In this regard, in order provide care which combines treatment requirements and easier access to services, Baxter is offering patients with Hemophilia And National Healthcare Systems a package of totally free home-care services (home-care services for patients affected by Hemophilia- Home Clinical Assistance (HCA); Home Rehabilitation Assistance (HRA); drug home delivery- Home Delivery Service; multimedia platform “B-nect/mobile patient care”). The cooperation

between a national healthcare system and a pharmaceutical company is a prime example of synergy aimed at serving patients’ interests, making healthcare expenditure more rational and curbing its scale, and pursuing a fair profit which is also ‘sustainable’. Such synergy must involve all stakeholders if it is to provide global assistance, with the patient at its center.

Pursuing this goal, Baxter has introduced, for the first time in the treatment of hemophilia, a risk-sharing policy providing for the sharing with the National Health System of expenditure resulting from case where immune tolerance programs with Advate are implemented.

Finally, several studies show that hemophilia significantly impacts on the QoL of hemophiliacs, especially due to disease-associated complications in terms of pain, joint disease and disability; furthermore, the emotional and psychological status of affected subjects is seriously impacted by the disease.

The introduction of prophylaxis and the availability of latest-generation clotting factors have provided these patients with the opportunity to improve their health profile and their QoL.

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## APPENDIX

LIST OF AICE CENTERS IN ITALY TAKEN FROM: LIST OF AICE CENTERS (17)		
<b>PIEMONTE</b>		
ALESSANDRIA	Centro Emostasi e Trombosi Dipartimento di Ematologia	Azienda Ospedaliera "SS. Antonio e Biagio"
TURIN	Centro Emostasi e Trombosi	SC Medicina Trasfusionale ed Ematologia
	Centro di Riferimento Regionale per le Malattie Emorragiche e Trombotiche Ereditarie in Età Pediatrica	Ospedale Infantile Regina Margherita
	Centro di Riferimento Regionale per le Malattie Trombotiche ed Emorragiche dell'adulto Divisione Universitaria di Ematologia	Ospedale Molinette
<b>LIGURIA</b>		
GENOA	Centro di Riferimento Regionale per le Malattie Emorragiche e l'individuazione del Rischio Trombotico Ereditario - Modulo Coagulazione ed Emofilia	Dipartimento di Emato - Oncologia Pediatrica IRCCS Giannina Gaslini
	Divisione Ematologia	Ospedale Galliera
<b>LOMBARDIA</b>		
BRESCIA	Clinica Pediatrica	Ospedale pediatrico universitario
CREMONA	Centro Emostasi e Trombosi	A.O. Istituti Ospitalieri
MILAN	S.S. Trombosi ed Emostasi Divisione di Ematologia	Ospedale di Niguarda ca' Grande
	Centro Emofilia e Trombosi e A.Bianchi Bonomi	Medicina Interna
	Clinica di Ematologia Pediatrica	Clinica Pediatrica de Marchi
PAVIA	Centro Emofilia e Coagulopatie Congenite	Policlinico S. Matteo
<b>TRENTINO</b>		
TRENTO	Centro Emofilia - Servizio Trasfusionale SIT	Ospedale S. Chiara
<b>VENETO</b>		
PADUA	Azienda Ospedaliera di Padova	Clinica Medica II
TREVISO	Servizio Trasfusionale-Centro Regionale Malattie del Sangue Servizio Assistenza Emofilia	Ospedale Civile
VERONA	Azienda Ospedaliera Universitaria Integrata - Verona	Servizio di Immunoematologia e Trasfusione - Centro Emofilia
VICENZA	Centro per lo Studio delle Malattie Emorragiche e Trombotiche	Dipartimento di Terapie cellulari ed Ematologia, Ospedale S.Bortolo

## LIST OF AICE CENTERS IN ITALY TAKEN FROM: LIST OF AICE CENTERS (17)

FRIULI		
UDINE	Centro Malattie Emorragiche e Trombotiche - SOC Medicina Trasfusionale	Az. Ospedaliero- Universitaria Santa Maria della Misericordia
EMILIA-ROMAGNA		
BOLOGNA	U.O. di Angiologia e Malattie della Coagulazione "Marino Golinelli"	Policlinico S.Orsola- Malpighi
FERRARA	Centro per l'Emostasi e la Trombosi Sezione di Ematologia	Arcispedale S. Anna
FORLÌ-CESENA	Servizio Trasfusionale	Ospedale Bufalini
MODENA	Divisione di Ematologia	Ospedale Policlinico
PARMA	Centro di Riferimento Regionale per la cura dell'Emofilia e delle Malattie Emorragiche Congenite Dipartimento Medico Polispecialistico	Azienda Ospedaliero-Universitaria di Parma
PIACENZA	Centro per la diagnosi delle Malattie emorragiche U.O. di Immunoematologia e Medicina trasfusionale	Ospedale di Piacenza
RAVENNA	Centro Emofilia Medicina Trasfusionale	Presidio Ospedaliero di Ravenna
	Centro Trasfusionale Faenza	Presidio Ospedaliero Faenza-Lugo
REGGIO EMILIA	Centro Emostasi e Trombosi I Divisione di Medicina Interna	Az. Ospedaliera di Reggio Emilia, Arc. Osp. S. Maria Nuova
TOSCANA		
AREZZO	Sezione di Ematologia	Ospedale San Donato
FLORENCE	Agenzia per l'Emofilia - Centro Regionale Riferimento Coagulopatie Congenite	Dipartimento DEA e Medicina generale e d'urgenza
UMBRIA		
PERUGIA	Centro Emofilia - Sezione di Medicina Interna e Vascolare-Stroke Unit	Ospedale Santa Maria della Misericordia
TERNI	Centro Emofilia Divisione di Medicina Generale	Ospedale S. Maria delle Stelle
MARCHE		
MACERATA	Centro di Riferimento regionale per i Difetti Ereditari della Coagulazione	Ospedale di Macerata
LAZIO		
LATINA	Centro Emofilia e Malattie Trombo-emboliche U. O. di Ematologia con Trapianto di midollo	Ospedale S. Maria Goretti
ROME	Divisione di Ematologia	Ospedale Pediatrico Bambin Gesù
	Servizio Malattie Emorragiche e Trombosi	Policlinico Universitario Gemelli
	Dipartimento di Biotecnologie cellulari ed Ematologia Sezione di Ematologia	Ematologia
	Serv. Ematologia e Trasfusioni	Università Tor Vergata

## LIST OF AICE CENTERS IN ITALY TAKEN FROM: LIST OF AICE CENTERS (17)

ABRUZZO		
L'AQUILA	Centro Emofilia e Trombosi Ematologia	Ospedale San Salvatore
PESCARA	Servizio Prevenzione e Cura Sindromi Emorragiche e Trombotiche Dipartimento di Ematologia	Ospedale Civile dello Spirito Santo
CAMPANIA		
NAPLES	Centro di Riferimento Regionale per le Emocoagulopatie Dipartimento Assistenziale di Clinica Medica	Azienda Ospedaliera Universitaria Federico II
	Centro di Riferimento Regionale Emocoagulopatie	Ospedale Pausillipon
	Centro Emofilia e Trombosi U.O. di Ematologia	Ospedale S.Giovanni Bosco
SALERNO	Servizio di Immunoematologia e Trasfusione	Ospedale S. Luca - ASL Sa/3
PUGLIA		
BARI	Centro Emostasi e Trombosi	U.O. Medicina Interna Universitaria "C. Frugoni" Ospedale Policlinico
	Azienda Ospedaliera Policlinico	U.O.S di Coagulazione (Emostasi e Trombosi)
LECCE	Centro Emofilia e Trombosi	U.O. di Medicina Interna - Presidio Osped. "I. Veris delli Ponti"
CALABRIA		
CATANZARO	Centro Emofilia. Servizio Emostasi e Trombosi	Ospedale Pugliese
COSENZA	Centro Emostasi e Trombosi	Ospedale Annunziata
REGGIO CALABRIA	Centro Emofilia Servizio Emostasi e Trombosi	Azienda Ospedaliera Bianchi Melacrino Morelli
SICILIA		
CATANIA	Centro di Riferimento Regionale per Emofilia e Trombosi, Modulo Dipartimentale Emofilia	Azienda Ospedaliera Universitaria Vittorio Emanuele, Ferrarotto, S. Bambino
PALERMO	Centro Regionale di riferimento "Emostasi e Trombosi in età Pediatrica"	Clinica Pediatrica
	Unità Malattie Tromboemboliche ed Emorragiche Divisione di Ematologia	Policlinico Universitario
SARDINIA		
CAGLIARI	Direttore Centro Emofilia	Istituto Clinica Pediatrica
OLBIA-TEMPIO	Centro Trasfusionale	Ospedale Civile di Olbia
SASSARI	Centro di riferimento regionale per le malattie emorragiche e trombotiche ereditarie in età pediatrica	Ospedale SS Annunziata - ASL1
	Centro Emofilia e Trombosi	Ospedale E. De Nicola

## 7. HTA of Advate in the treatment and the prophylaxis of Hemophilia A: ethical considerations

*Maria Luisa Di Pietro*

### PRELIMINARY REMARKS

Hemophilia A is an X-linked disease, characterized by insufficient levels of factor VIII (FVIII). Clinical manifestations of the pathology are spontaneous bleeding in the joints, muscles and internal organs (1) or bleeding following trauma, tooth extractions or surgical intervention. Previous chapters have shown how these bleeding episodes, when not treated promptly, can lead to permanent outcomes such as the loss of articular mobility and consequent disability, and – in the most severe and acute forms – even to death.

Hemophilia is, therefore, a severely debilitating disease, whose incidence in the European Union alone is 0.6 per 10 000, totaling approximately 30 000 cases. This entails significant economic and human costs and has a considerable social impact.

The management of Hemophilia A has evolved greatly over the years, leading to an ongoing and overall improvement in the quality of life of hemophilic patients. In chapter 6, which dealt with the organization of healthcare assistance, we pointed out how, thanks to strategies of de-hospitalization and home-care treatment, facilitated by the issuing of appropriate laws on home self-transfusion, hemophilic patients are becoming less and less dependent on the treatment centers (2). The evolution of pharmacological therapy, dealt with in Chapters 2 and 4, has been rapid: from blood transfusions to FVIII plasma derivatives and highly purified (pdFVIII) derivatives to the present-day concentrates of recombinant FVIII (rFVIII) used on demand (in the treatment of bleeding episodes) or in prophylaxis (with continual and regular infusion to prevent the onset of bleeding and articular damage) (3, 4) or used to guarantee hemostatic cover during/after a surgical intervention.

Prophylaxis may be primary, if the medicine is administered before the insurgence of damage to the joint, or secondary, where articular damage has already taken place and the interest is in preventing its progression (5, 6) (see Chapters 2 and 4).

The use of recombinant products has improved the safety of treatment while at the same time guaranteed levels of efficacy equal to that of plasma-derived products. Yet, as was emphasized in Chapter 2 on treatments, first-generation recombinants did not eliminate completely two risks:

1. The development in the hemophilic patient of inhibitors: that is, of antibodies that neutralize the rFVIII infusion, and whose presence reduces the efficacy and increases the cost of treatment (7);
2. The risk of transmission of infective agents through the use – albeit limited – of plasmatic proteins of animal origin, even in the absence of infections such as HIV or HCV, as used to happen with derivatives of human origin (8).

The aim of research has therefore been to producing a drug that could meet both these needs. This led to the development of Advate, the subject of these ethical considerations, as part of the HTA process.

The ethical analysis in an HTA process must, however, take account of the multiplicity of possible approaches. If an approach is to fulfill the task, it must possess the following requisites: a) It must have an appropriate methodology; b) It must make reference to an ethical theory that can relate the unity of a set of fundamental principles to the plurality of different possible decisions; c) It must make a distinction between the objective plane of the consequences of decisions to be taken and the subjective plane of the evaluation of circumstances (9).

In this contribution, the ethical analysis, which proceeds from cognitive-objectivist type perspective, will make use of so-called 'method triangulation': an epistemological view will be followed in turn by a value analysis and then by an evaluation (10).

## EPISTEMOLOGICAL VIEW

Advate, which is comprehensively presented in Chapter 4, is an FVIII concentrate derived from recombinant DNA (rFVIII; INN: octocog alfa), produced without the use of human or animal plasmatic protein in the cell culture, purification and final formulation processes (third-generation rFVIII) (11). Marketed in December 2004, Advate is indicated for the treatment and the prophylaxis of hemorrhages in Hemophilia A patients. Administration method (by continuous infusion or in bolus) and dosage vary according to whether the drug is used to prevent or to treat a bleeding episode, and according to severity of hemorrhaging (12).

Advate is presented as an innovative treatment for the following reasons: 1. The total elimination of the transmission of pathogenic agents transmitted by plasmatic proteins; 2. Its low immunogenicity among previously treated patients; 3. The availability of the widest range of formulations and its usefulness at room temperature for a maximum period of six months, both of which characteristics enable treatment to be personalized, with a possible increase in compliance with therapy.

Advate still today remains the only recombinant product with a full-length FVIII molecule, analogous to native FVIII (see Chapter 4).

## VALUE ANALYSIS

The ethical analysis in the HTA process on Advate cannot dispense with an anthropological clarification of values: that is, a review of the notions of humanity, life, health, freedom and justice to which we refer. A purely procedural approach would not ground the justification of moral values, principles and norms in a rational way, and would lead us to a merely arbitrary procedure and a conceptual elaboration that merely aims to solve practical issues (13). The working through of a single case must always refer back to ultimate reasons – among them moral values and principles – that provide the orientation of our choices.

In this ethical analysis during an HTA process, reference will be made, as mentioned above, to a cognitive-objectivist perspective that proceeds from the recognition of a person's being and dignity as absolute values, and which places the unconditional respect of their inviolability as a first principle (14). It follows from this that the defense of physical life, the promotion of health and the quality of life, the respect of free and responsible choices, the seeking after the common good, are fundamental values with their own hierarchy among them. In the biomedical field, and therefore also in an HTA process, the adoption of this approach translates into the evaluation of the impacts that the use or the introduction of health technologies will have on the overall good of humanity.

## The risk/benefit relationship

Within the remit of defending physical life, the first element to analyze when faced with a proposed new technology is whether the risk of negative effects is balanced or not by expected benefits to the patient. We must, therefore, evaluate – on one hand – the clinical indication, drawing on support from the findings of controlled random clinical trials (RCTs) and tests of efficacy, along with the study of meta-analyses, and – on the other – analyze the foreseeable risk/benefit relationship.

The main clinical studies on Advate, which was shown in the preclinical phase to be bioequivalent to anti-hemophilic recombinant factor (Recombinate® -Baxter), have been amply discussed in Chapter 4 of this report. They showed how the product is safe and efficacious, well tolerated and with a low level of immunogenicity both in adult and in the hemophilic patient in pediatric age, when used in prophylaxis and in the control of traumatic, bleeding episodes (15, 16) or intra/post operatively (17). The same Chapter 4 also reports evidence of a low and non-persistent incidence of inhibitors and an adequate risk/benefit relationship. Among the most common collateral effects are: alterations of the sense of taste, dizziness, headaches, fever, abdominal pains and diarrhea (18). These results appear to have been confirmed by phase 4 studies, principal among which was the Advate PASS surveillance which involved previously treated hemophilic patients (PTPs) and found an appreciably low immunogenicity (19).

### Quality of life

Previous chapters have highlighted how the best results are to be expected from prophylaxis of bleeding episodes and, especially, from primary prophylaxis in children, when initiated before three years of age, as well as from secondary prophylaxis in adolescents and adults. The choice of treatment regime with Advate, whether on-demand or in prophylaxis, depends both on the treatment objectives for the individual hemophilic patient and, to no lesser extent, on the healthcare resources available (see Chapters 2 - 6).

Prophylaxis enables bleeding episodes to be prevented, thereby eliminating or minimizing articular damage and the onset of conditions of permanent and grave impairment (see Chapters 2 and 4) (20, 21). What follows is not only the improvement of the quality of life for the hemophilic patient, but also the reduction of social costs for healthcare, treatment and rehabilitation (see Chapters 3 and 5) (22). On the other hand, dependence, life-long, on continuous treatment, as well as possible limitations due to articular complications, can negatively influence the psychological condition of the hemophilic patient (23, 24).

To this must be added the opportunity, by using prophylaxis, of having a normal social life, as a better health profile reduces the number of absences from school (25) or from work, and of having a normal family life, especially where a suitable management at home is possible and where the hemophilic patient and their family can be offered a program of care. The home-based prophylactic administration of rFVIII with assistance from specialized personnel, allowing families to manage the therapy autonomously, is indeed a great benefit (see Chapter 6).

### Respect of the autonomy of the patient

Respecting a patient's autonomy means putting them in a position to choose what is the best option for the improvement of their own condition and quality of life. This requires an adequate process of communication, within which the necessary information can be offered and consent obtained, while striving to remove all the obstacles that impede such an expression of autonomy on the part of the patient.

The hemophilic patient should be informed

of the difficulties and the possible risks deriving from taking Advate and the expected results of treatment (referring both to the international literature and to the personal case-history experience of the specialist) as well as of the therapeutic alternatives. The patient should also be informed of the correct method for taking the medicine (to avoid a drop in its efficacy – especially in prophylactic terms – which may derive from the interruption of the treatment) and of the risks connected with the lack of prophylaxis of bleeding episodes. The communication process provides, in fact, the suitable 'venue' both for motivating towards prophylaxis and for removing possible barriers.

Previous chapters have shown how prophylactic treatment of hemorrhagic episodes requires, on the one hand, the involvement of the hemophilic patient and of their carer (especially in the case of a minor), and on the other hand, the efficacy, safety, availability and practicality of the product used (see Chapters 2-6). Moreover, the elimination of the risk of pathogenic transmission increases both the confidence of the hemophilic patient in the safety of the product and its long term economic benefits. The study in Chapter 3 of the pharmaceutical-economic models of costs associated with co-morbidity showed that hemophilic patients infected with HIV and HCV cost more to manage than uninfected patients, because they require longer periods of hospitalization, more frequent medical and specialist outpatient examinations and the use of long-term health resources (26).

The advantage sought by prophylaxis, i.e., improvements in articular and musculo-skeletal conditions and in psychosocial development, especially of the child, should be a more than sufficient as reasons for the removal of possible 'barriers' to its use (difficulties with venous access; non-compliance with the treatment; costs), which are responsible for the non-commencement or suspension of such treatment (27).

An important role in providing motivation for this therapy can be played by the physician at the Hemophilia Centre, who will evaluate with the hemophilic patient, and/or their parents, the possible appeals of one treatment over another, comparing risks and benefits and explaining clearly the correct mode of administration, taking steps to start organizing home assistance (a theme that was amply developed in Chapter 6). It will also be

the physician's task to provide motivation for prophylaxis, especially among families with low compliance (due to psychological difficulties, fear of collateral effects, conviction that it is necessary to intervene only in the acute phase, etc.), and among those with a modest socio-economic level.

### THE QUEST FOR THE COMMON GOOD: A QUESTION OF JUSTICE

Hemophilia A is a rare disease, whose social and clinical management is complex and economically demanding. As previous chapters have argued, in calculating its total costs, it is necessary to itemize not only the costs of specialist and non-specialist outpatient treatment, diagnostic tests, hospitalizations and psychological assistance, but also, and especially, the cost of drugs (see Chapters 3 and 5) (28, 29).

This consumption of resources becomes even greater where the hemophilic patient develops inhibitors, with the inevitable increase in the number of days of hospitalization and treatment of the complications that can no longer be prevented. These are not simply economic costs, but above all human ones in terms of pain, disability and suffering (see Chapters 2 and 3).

The cost-benefit relationship cannot be given priority over the risk-benefit relationship in an absolute way. In a cognitive-objectivist approach, the primary objective is to achieve improvement in the condition and quality of life of the patient. It is to this end that all of the energies of healthcare operators and those who manage public health must be aimed. Faced, however, with limits to the available economic resources, we cannot avoid addressing the problem of costs. What should our reference parameters be here?

First of all comes respect for the individual needs of each patient: recognizing what they deserve objectively for their conditions of health, and what conditions of health are their due because of their intrinsic dignity (30). It follows that, faced with questions relative to health; we must look for a morally justified criterion for the selection of priorities, so that everybody will be offered equal opportunities for reaching their maximum health potential within their age group.

Chapter 6 has shown how treatment of

hemophilic patients requires adequate healthcare assistance. Despite differences between regions, moves in this direction have in fact already begun. The added possibility of decentralizing the place of care, favoring de-hospitalized home management, would bring a further improvement of to the quality of life of the hemophilic patient and a reduction in the costs of healthcare assistance. This is especially the case where treatment is prophylactic (31) and not on demand (see Chapter 6).

This holds a double benefit: a human benefit, in terms of the reduction of dependency, suffering and lack of self-sufficiency from bleeding episodes and their sequelae, which is in turn also an economic benefit. Having, finally at our disposal, treatments capable of nullifying the incidence of infections (for example, from HIV and from HCV) and of minimizing the development of inhibitors, allows us a vision of a promising solution.

This solution must, however, fulfill two conditions: 1. It must guarantee to the hemophilic patient continuity of treatment and of help with self-management of the disease and with home assistance. 2. It must involve the physician at the Hemophilia Centre and a psycho-pedagogical team in the management of the disease and of its treatment (an important role could be played by a clinical educator in the case of a developing patient). This last point becomes a very central one with the move towards prophylactic care, whose strong point is its involvement and motivation, therefore through psycho-pedagogic intervention, of the hemophilic patient and their family.

### ETHICAL EVALUATION

In conclusion, considerations of safety, tolerability and efficacy in terms of prophylaxis and of the therapy of bleeding episodes would appear to support the use of Advate.

In order, over and above this, to guarantee the correct use of Advate, decision makers should undertake the following steps:

1. They should organize continuous treatment procedures (specialist center - home care) whereby the clinical situation of each individual hemophilic patient can be reviewed and their therapy adapted appropriately.
2. They should verify opportunities for and the feasibility of providing equal access to



- the drug for all patients with Hemophilia A.
3. They should require of the physicians at the Hemophilia Centers that they practice particular care in checking the drug's efficacy and in monitoring any signs of adverse events.
  4. They should promote forms of

comprehensive assistance (including psycho-pedagogic) at the home level of the hemophilic patient and their family.

5. They should interact with the responsible institutions to obtain better organization and healthcare-assistance cover across the whole of the national territory.

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## 8. Key points for decision-makers

Chiara de Waure, Walter Ricciardi

1. Hemophilia A is a hereditary blood disorder caused by a deficiency of factor VIII (FVIII), whose gene is localized on the X chromosome.  
According to estimates by the World Federation of Hemophilia (WFH), there are approximately **110 000 cases worldwide**. In **Italy**, according to estimates by the National Register of Congenital Coagulation Disorders, there are **approximately 4 000 patients with this disease**, half of whom are cases of severe hemophilia (functional FVIII <1%). **Thanks to improvements in healthcare, an increase in prevalence at a national level is to be expected**; assuming that incidence of the disease remains constant over time.
2. Patients with Hemophilia A are treated with **the infusion of FVIII**. Therapy can take place **on-demand**, during a bleeding episode, or **for prophylactic ends**, to reduce the risk of articular damage. According to the WFH, **primary prophylaxis** (continuous long term treatment begun after the first episode of intra-articular bleeding and before two years of age) **constitutes the gold standard**. Substitution therapy, following the guidelines of the Italian Association of Hemophilia Centers, should take place **preferably using recombinant products**, where these are available. The latter are obtained using recombinant DNA technology and can be subdivided into first, second- and third-generation products, according to the presence of plasma-derived animal and human proteins used as an additive on the culture medium and/or as a stabilizer. **From the point of view of efficacy, all products have a good profile, although newer generation products guarantee higher levels of safety in terms of potential infections**. The issue of the development of inhibitors remains to be resolved; this can affect up to 30% of patients and can require the activation of specific therapeutic protocols for the induction of immune tolerance (ITI).
3. Looking at the consumption of economic resources, **the infusion of FVIII constitutes the main cost driver** (97-98% of the total); this is followed by the spending associated with hospitalizations, by other costs and by diagnosis. **Mean annual costs per patient** vary in Italy between **€150 133.19 and € 248 413.19**, depending on the type of pharmacological treatment (plasma derivatives or recombinant products of second and third generation). The protocols based on recombinant factors are in fact characterized by higher yearly costs than those based on plasma derivatives. The mean annual cost per patient increases in case of inhibitors, being 98.3% of costs due to pharmacological treatment. With regard to the impact of costs of inhibitors on public expenditure, it would be desirable to choose therapeutic alternatives at lower risk of inhibitor development.
4. Launched on the market in 2004, **Advate®**, **FVIII recombinant**, remains the only FVIII recombinant **with a full-length molecule** that is produced completely without the use of human or animal plasmatic protein. It guarantees to the patient **the highest safety level** with respect to the risk of infection. The structural integrity guarantees the clinical efficacy of the product, as demonstrated in clinical practice through the wide pre- and post-authorization development plan. This same structural integrity could, moreover, be decisive for the product's **low immunogenicity**: that is, its reduced potential for the development of inhibitors, as has been shown by the results of the clinical development plan and confirmed in previously treated patients during the post-marketing PASS surveillance study.
5. The economic analysis focused on the use of Advate® on-demand versus in prophylaxis. The results show that prophylaxis is effective in comparison to on-demand strategy at reasonable higher

costs. **The incremental cost-effectiveness ratio (ICER)** of prophylaxis with Advate® is equal to €35 036 per QALY gained, and may be considered acceptable because hemophilia is a rare disease. The sensitivity analysis shows, however, a certain degree of instability in this estimate, which leads to a need for further economic assessment studies that can better estimate the impact on efficacy and costs, possibly with a breakdown according to patient category and disease severity.

6. Treatment of the hemophilic patient requires a **multidisciplinary approach and a complete and reliable collection of epidemiological and healthcare data** for the purposes of proper planning and healthcare programing. **Regional and national registers therefore constitute a fundamental instrument and are important** for interventions aiming to improve the management of congenital coagulation disorders. It is, moreover, necessary to have an articulated organization of the centers of diagnosis and hemophilia treatment, so that these are able to ensure **a multiplicity of services** (24-hour availability, hospitalization, check-up examinations, psychological counseling, and training for home treatment, genetic counseling and diagnosis) for the purpose of **the standardization of these services**. With regard to the healthcare assistance, **compliance with prophylaxis regimes can be facilitated by specific home assistance programs**. In the context of de-hospitalized treatment, this mode of healthcare, if properly monitored by the referring clinicians, can guarantee a completely normal life to the hemophilic patient. Home-care activity should nonetheless be accompanied by the use of a team of specialized health operators,

trained specifically for the purpose, able to instruct, supervise and support the patient and their family in home-care management/self-management, until they reach complete autonomy.

7. In this connection, in order to implement its health-care **offer, Baxter is placing at the disposal of hemophilic patients and the Public Health Service a package of totally free home services** (home-care service for the hemophilic patient **Home Clinical Assistance (HCA)**; a home physiotherapy service **Home Rehabilitation Assistance (HRA)**; a service of home delivery of the medicines **Home Delivery Service (HD)**; a multimedia platform **“B-nect/mobile patient care”**; a service of assisted therapy with animals **Equine therapy**; a service of psychological support **Home Psychological Assistance (HPA)**). **This collaboration between the National Health Service and the pharmaceutical Company represents an example of synergy in the interests of the patient**, aimed at the rationalization/containment of healthcare expenditure and at the pursuit of fair and ‘sustainable’ profits. Following this principle, Baxter has introduced for the first time in hemophilia care, importing it from other therapeutic areas, a policy of risk sharing, offering to share in the costs with the National Health Service in case an induction of immunotolerance program with Advate® is used.
8. **The safety, tolerability and efficacy** both in terms of prophylaxis and of the **therapy of bleeding episodes achievable with Advate® enables us to issue an overall favorable ethical judgment. It is nonetheless advisable that decision makers** work to support **continuity of care, multidisciplinary approach and equality in the access to health services**.



# ASSESSMENT OF THE CLINICAL AND ECONOMIC IMPACT OF ADVATE IN PROPHYLACTIC TREATMENT OF HEMOPHILIA A PATIENTS

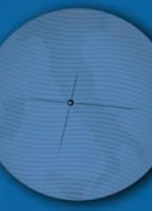
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## UPDATE

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# Introduction

## INTRODUCTION

Health Technology Assessment (HTA) is a cyclical process that requires updates and revisions of previous publications (1). Thus, the decision to update Advate HTA arises from the presence of new data (2). The update refers to:

1. *Efficacy and safety of treatment with Advate;*
2. *Pharmacokinetics and dosage of Advate and potential economic repercussions;*
3. *Treatment options based on pharmacokinetics;*
4. *Economic evidence on product safety;*
5. *Hemophilia management and the optimization of services offered by the company.*

Before reviewing new evidence regarding the above points, we briefly list the conclusions (3) of the assessment carried out in 2010 and published in 2011. Hemophilia A is a hereditary disease caused by a deficiency of coagulation factor VIII (FVIII). The main symptom is bleeding, at times resulting in joint damage or even death. Approximately 4 000 people suffer from the disease in Italy and around half of these have the severe form of Hemophilia A (functional FVIII < 1%). Treatment of patients with Hemophilia A consists in infusions of FVIII. The guidelines of the Italian Association of Hemophilia Centers state a preference for therapy using recombinant products, when these are available. These products are divided into first-, second- and third-generation products depending on the use of human and animal protein as additives to the culture medium and/or as stabilizers. The different product classes are almost identical in terms of efficacy, but third-generation products (Advate and ReFacto AF) guarantee a higher level of safety thanks to the fact that they are free from animal protein. Advate is the only full-length recombinant FVIII that is produced without the addition of plasma or albumin. The clinical evidence derived from

pre – post authorization studies has demonstrated that Advate’s intact protein, which distinguishes it from Refacto AF, provides a guarantee of its efficacy. This structural integrity is also the basis of Advate’s low immunogenicity, i.e. a lower probability of developing inhibitors. Inhibitor development occurs in up to 30% of patients and special treatments have to be set up in these cases to induce immune tolerance, hence an increase in costs.

FVIII infusions can be administered on demand, when bleeding occurs, or as a continuous long-term prophylactic treatment regimen. Infusion costs make up 97-98% of total annual costs per patient, which vary in Italy between € 150 133.19 and € 248 413.19, depending on the type of pharmacological treatment used (plasma-derived or recombinant products).

With reference to the treatment regimes, both the World Federation of Hemophilia (WFH) and our pharmaco-economic assessment have come out in favor of prophylaxis as the gold standard for treatment. Prophylaxis can reduce bleeding episodes and the associated sequelae to acceptable costs. Our economic comparison between treatment approaches showed a value of €35 036 per additional QALY for prophylactic treatment with Advate compared to on-demand administration of the same product. This is an acceptable value considering the rarity of the disease. Moreover, for integrated and multidisciplinary patient management, our previous report showed how the Company can provide several home-care services that are free of charge to patients. These include nursing care and physiotherapy, drug delivery, psychological support and online medical services as well as recreational activities with animals. The economic value of these services will be outlined in this update. The Company has also adopted a policy of Risk Sharing by sharing the costs of Advate’s immune tolerance programs with the National Healthcare Service (SSN), making this a further example of public-private cooperation.



# 1. Efficacy and safety of treatment

The clinical development program and the post-marketing studies on Advate have demonstrated that the product is effective and safe to use both for on-demand patients and for those in prophylactic therapy as well as for patients undergoing surgery (4). During the past year, two new important clinical studies have confirmed the product's high level of efficacy and low immunogenicity (Table 1); the results of these studies (5-6) are summarized below.

## AUERSWALD 2012

In 2012, Auerswald and colleagues (5) published the results of an international open-label, multi-centric prospective trial aimed at assessing the efficacy and safety of Advate for Previously Untreated Patients (PUPs).

### Study design:

- 55 patients participated in the study; 44 of these completed the protocol
- Of the 55 initial patients, 18 were PUPs and 37 minimally treated patients (MTPs). The median age was 7 months
- 96% of patients had a level of FVIII  $\leq 1\%$
- Advate was administered following a standard prophylaxis schedule (25-

50 IU/kg 3-4 times per week), or a modified prophylaxis schedule (dosage or frequency of administration at the clinic's discretion, but different from those used in the standard schedule). Alternatively, a combination of these two regimens was used

- The follow-up included 75 days of exposure to the product or, alternatively, treatment over a 3-year timeframe

### Results of the study:

- The hemostatic efficacy of Advate was considered excellent or good in 93.4% of assessments
- 90% of the episodes of bleeding were resolved using 1-2 Advate infusions and in 69% of cases a single infusion was effective
- The incidence of inhibitors was 29%, in line with available evidence on this type of patient (PUP)
- A close correlation was found between risk factors for inhibitor development and the actual development of antibodies
- No adverse reactions linked with the use of Advate were found

This study confirms the efficacy and safety of Advate in the treatment of PUPs with severe

TABLE 1

CHARACTERISTICS OF MAIN STUDIES ON THE EFFICACY OF ADVATE

Phase III pilot (Tarantino, 2004)	Assessment of pharmacokinetics (double-blind, randomized, cross-over), safety, immunogenicity and hemostatic efficacy (open-label) in a European and U.S. cohort of PTPs $\geq 10$ years
Follow-up (Group 2006)	Assessment of pharmacokinetics, safety, immunogenicity and hemostatic efficacy (open-label) in PTPs that have continued the pilot study
Surgery (Negrier 2008)	Assessment of pharmacokinetics, immunogenicity and hemostatic efficacy (open-label) for post-operative management of a European, U.S. and Canadian cohort of PTPs $\geq 5$ years
Pediatric PTPs (Blanchette 2008)	Assessment of pharmacokinetics, safety, immunogenicity and hemostatic efficacy, including perioperative management (open label), in a European, U.S. and Canadian cohort of PTPs $\leq 6$ years
PUP Study (Auerswald 2012)	Assessment of pharmacokinetics, safety, immunogenicity and hemostatic efficacy (open-label) in a global cohort of PUPs $\leq 6$ years
Prophylaxis Study (Valentino 2012)	Assessment of efficacy and immunogenicity in two prophylactic regimens and on-demand treatment of PTPs

PTP: Previously Treated Patients; PUP: Previously Untreated Patients



or moderate Hemophilia A. It also shows that inhibitor development in PUPs is closely related to other intrinsic (genetic, immunological, ethnic, familial, etc.) and environmental factors that predispose to risk.

## VALENTINO 2012

The Prophylaxis Study Group recently published data from a prospective, multi-centric, open-label study which aimed at evaluating in PTPs the efficacy of standard prophylaxis with Advate, of PK prophylaxis, where dosage and frequency of administration were based on pharmacokinetics, and of on-demand treatment (6).

### *Study design:*

- 82 patients recruited with >150 exposure days, of whom 73 received treatment
- Baseline FVIII levels < 1%
- Initial on-demand treatment for 6 months, followed by a randomized standard prophylactic regimen (32 patients, 20-40 IU/kg every 48 hours) or by a pharmacokinetic prophylaxis (34 patients, 20-80 IU/kg every 72 hours)
- Prophylaxis duration: 12 months

### *Study results:*

- Efficacy in terms of Annual Bleeding Rate (ABR) was similar for both prophylactic regimens with a 99.4% reduction ( $p < 0.0001$ ) compared to on-demand treatment
- Hemostatic efficacy was excellent or good in 78%-89% of assessed cases
- 70% of bleeding episodes were resolved by a single infusion
- Compared to on-demand treatment, prophylactic treatment with Advate, either standard or based on pharmacokinetics, was linked to a significant reduction of pain and an improvement of the physical condition of patients
- The efficacy data show that a pharmacokinetic prophylactic regimen can be adopted for patients that are being treated with Advate, reducing the number of weekly administrations (20–80 IU/kg every  $72 \pm 6$  h with pharmacokinetic prophylaxis versus 20–40 IU/kg every  $48 \pm 6$  h, with standard prophylaxis)
- No patients developed inhibitors



## 2. Pharmacokinetics, dosage and possible economic repercussions

Studies carried out to date appear to suggest possible differences in clinical efficacy between products based on full-length-molecule FVIII (FL-FVIII) – like Advate –, and products lacking the molecule's B domain (B domain deleted – BDD-FVIII) - ReFacto AF – (4). The reasons behind the periodic lack of hemostatic response in BDD products may be found in the half-lives of these products. Collins et al. have in fact demonstrated that product half-life and weekly frequency of administration are key factors for maintaining a trough-level of FVIII > 1% in patients undergoing prophylactic treatment. This level is considered to be sufficient to prevent episodes of bleeding and their consequences (4).

The previous report already provided evidence of a longer half-life of Advate than of BDD-FVIII (4). This aspect was recently considered by Johnston (7), who collected all available evidence regarding possible differences between FL-FVIII and BDD-FVIII. The conclusion of this research was that the lower efficacy of BDD-FVIII in prophylaxis can reasonably be attributed to the product's shorter half-life (a difference of almost 2 hours: 13.3 for Advate and 11.2 for BDD-FVIII Moroctocog alfa). The author estimates that, compared with Advate, a 68% increase in ReFacto AF consumption is required in order to reach the same plasmatic levels of FVIII.

This result could have repercussions on product consumption. The analysis by Epstein et al. (8), referring to consumption data of pharmaceutical products among a cohort of 1 011 hemophilia patients, shows that patients receiving prophylactic treatment with BDD-FVIII consume on average 33% more product per year than patients treated with FL-FVIII. This is equivalent to an average kg-per-year consumption of 4 580 with BDD-FVIII and of 4 011 IU (3 551 IU in the subanalysis based on paired data) with FL-FVIII. The authors explain that more BDD-FVIII has to be administered due to an increase in the requirement for FVIII, despite the fact that the prescribed doses for both products are similar. More recently, a consumption analysis carried out on a cohort of 44 patients in prophylaxis in the UK

demonstrated that switching from prophylactic treatment using FL-FVIII to treatment using BDD-FVIII led to a 20% increase in consumption (9).

This evidence would appear to suggest that treatment with BDD-FVIII is more expensive. However, in order to corroborate these findings, the related impacts on patient health would need to be studied.

The studies cited above make it possible to estimate the costs of treatment with Advate (FL-FVIII) and with ReFacto AF (BDD-FVIII) based on prices in Italy. Considering the consumption levels found by Epstein et al. (8) and using an estimate of costs of treatment with Advate in Italy, the higher consumption of ReFacto AF leads to the cost differentials illustrated in Table 2, subdivided according to four types of patients (based on age and dose).

Median ReFacto AF consumption is shown to be 12%-29% higher than Advate consumption. With a price per IU of €0.69 for ReFacto AF and €0.75 for Advate, a 16% annual cost saving per patient can be reached under hypothesis 1 and 3% considering hypothesis 2. In absolute terms, savings range from €16 000 to €61 000 and from €3 000 to €11 000 respectively (Table 2).

Although the data used originate from the USA, and should therefore be compared with any relevant data available in Italy, the findings supporting this calculation have been given considerable support from a theoretical perspective by Johnston's study (7). Johnston estimates the relationship between the half-lives of Advate and ReFacto AF and the doses of each that are required to keep FVIII levels on or above 1IU/dl.

The ratio between required doses of ReFacto AF (shorter half-life) and Advate (longer half-life) increases exponentially by a factor that depends on the difference between the two half-lives. It is possible therefore to calculate the relationship between the required doses of the two products as a function of their frequency of administration. Clearly, as the length of the interval between administrations increases, the required dosage of the product with a shorter half-life will increase more than proportionately. Table 3

TABLE 2

COSTS OF TREATMENT WITH ADVATE AND REFACTO AF, BASED ON EPSTEIN (8)			
HYPOTHETICAL CASE 1: MEDIAN ANNUAL CONSUMPTION PER KG OF 4 580 IU WITH BDD-FVII AND 3 551 IU WITH FL-FVIII			
	REFACTO AF	ADVATE	% AND € Δ (R-A)
Use of the product in prophylaxis (median IU/kg/year)	4 580	3 551	29%
Adult, minimum dose	€ 242 955	€ 204 750	€ 38 205
Adult, maximum dose	€ 388 729	€ 327 600	€ 61 129
Child-adolescent, minimum dose	€ 104 124	€ 87 750	€ 16 374
Child-adolescent, maximum dose	€ 166 598	€ 140 400	€ 26 198
HYPOTHETICAL CASE 2: MEDIAN ANNUAL CONSUMPTION PER KG OF 4 580 IU WITH BDD-FVII AND 4 011 IU WITH FL-FVIII			
Use of the product in prophylaxis (average IU/Kg/year)	4 580	4 011	12%
Adult, minimum dose	€ 211 772	€ 204 750	€ 7 022
Adult, maximum dose	€ 338 836	€ 327 600	€ 11 236
Child-adolescent, minimum dose	€ 90 760	€ 87 750	€ 3 010
Child-adolescent, maximum dose	€ 145 215	€ 140 400	€ 4 815

Refacto € 0.69 IU; Advate € 0.75 IU

TABLE 3

COSTS OF PROPHYLACTIC TREATMENT WITH ADVATE AND REFACTO BASED ON FREQUENCY OF ADMINISTRATION (7)						
					EURO 2012	
	ADVATE DOSE	REFACTO AF DOSE	REFACTO AF COSTS	ADVATE COSTS	Δ (R-A)	
ADMINISTRATION EVERY 48 H DOSE CONVERSION FACTOR ADVATE-REFACTO AF OF 1.85						
Adult, minimum dose	273 000	505 050	€ 348 485	€ 204 750	€ 143 735	41%
Adult, maximum dose	436 800	808 080	€ 557 575	€ 327 600	€ 229 975	
Child-adolescent, minimum dose	117 000	216 450	€ 149 351	€ 87 750	€ 61 601	
Child-adolescent, maximum dose	187 200	346 320	€ 238 961	€ 140 400	€ 98 561	
ADMINISTRATION EVERY 72 HOURS DOSE CONVERSION FACTOR ADVATE-REFACTO AF OF 2.53						
Adult, minimum dose	273 000	690 690	€ 476 576	€ 204 750	€ 271 826	57%
Adult, maximum dose	436 800	1 105 104	€ 762 522	€ 327 600	€ 434 922	
Child-adolescent, minimum dose	117 000	296 010	€ 204 247	€ 87 750	€ 116 497	
Child-adolescent, maximum dose	187 200	473 616	€ 326 795	€ 140 400	€ 186 395	

Refacto € 0.69 IU; Advate € 0.75 IU.

shows treatment costs in relation to frequency of administration for the previously described four types of patient.

These results were obtained using the formula put forward by Johnston (7), which states that, compared with the product with a longer half-life, the dose of FVIII with a shorter half-life should increase by 85% in the case of administration every 48 hours and by 153% when administered every 72 hours.

These findings, if applied to the comparison between ReFacto AF and Advate, would lead to cost savings of 41% and 57% respectively if Advate is used. However, these results require further assessment and verification and, most importantly, need to be adjusted to the situation in Italy, particularly in view of the fact that more than double doses of FVIII are unlikely to be found in the medical practice of any country.



### 3. Possibilities and potential of treatment based on pharmacokinetics

As described above, prophylaxis is considered to be the optimum treatment for the management of Hemophilia A patients. This involves FVIII infusions three times per week. As also noted above, the study by Valentino et al. (6) published in 2012 compared the efficacy of two prophylaxis regimens using Advate in a controlled and randomized clinical trial. Concentrates were administered at a 20-40 IU/kg dose (standard prophylaxis) three times per week, versus a prophylactic regimen in which dosage and administration frequency was based on pharmacokinetics (20-80 IU/kg) (PK-tailored).

No statistically significant differences between the two regimens were found in the trial in terms of efficacy, expressed in annualized bleeding rate, with a mean of 1.6 ( $\pm 1.2$ ) for patients treated with standard prophylaxis and 1.9 ( $\pm 1.1$ ) for patients treated with PK-tailored prophylaxis ( $p=0.26$ ). Advate consumption, rate of adverse events and safety were similar in both cases. It should however be pointed out that Advate consumption was lower (although this was not statistically significant) in the PK-tailored regimen, with an average annual uptake of 5 768.2 IU/kg (inter-quartile range 1 697.4) against 5 197.8 (5 005.1) respectively.

Therefore, the use of Advate in PK-tailored prophylaxis appears to offer another valid option in addition to standard prophylaxis

treatment for the prevention of bleeding episodes. Although no significant difference was found in Advate consumption between the two cases, the lower number of infusions (one fewer per week) could increase treatment compliance, particularly for adolescent and adult patients, for whom long-term compliance remains a challenge. Apart from its possible impact on compliance, the lower number of infusions may also have a positive impact on quality of life and indirect costs, although no statistically significant differences between the two regimens were found in the Health-Related Quality of Life assessment. Nevertheless, the measurement of Quality of Life has been demonstrated an important step in the evaluation of Hemophilia patients (10).

The study nonetheless supports the adoption of an optimized Advate prophylactic regimen based on pharmacokinetic response. Despite having a lower frequency of administration than normal prophylaxis, such a regimen appears to be effective in preventing bleeding episodes and therefore in improving patients' quality of life. The possibility of optimizing prophylaxis by reducing frequency of administration and calculating dosage on the basis of pharmacokinetic response has already supported by other findings (6-9, 11), but this remains to be verified through targeted studies.



## 4. Economic evidence relating to product safety

Safety and inhibitor development are among the most important issues when considering which class of molecule should be used in prophylactic treatment of hemophilia patients. We therefore think it is appropriate to discuss some evidence taken from the grey literature.

Fourth Hurdle Consulting Ltd (12) has attempted to define the infection risk threshold at which Advate becomes cost-effective, with a value of €45 000 per QALY gained, compared to second-generation recombinant products. This assessment was included in the dossier presented to the Swedish Pharmaceuticals Benefits Agency. Cost and utility data regarding five types of blood-borne infections (HIV, hepatitis C (HCV), Creutzfeldt-Jakob disease (vCJD), West Nile virus and Parvovirus B19) were entered into the model. The results take into account pediatric patients (3-18 years old) and compare the use of Advate, considered to be a product with zero risk of transmission, with the use of second-generation products. As is known, the fact that no human and/or animal products are added in any stage during Advate's production effectively eliminates the product's risk of transmitting any blood-borne pathogens, be they known, unknown or emergent (13). Such a risk cannot be excluded with second-generation products, although little evidence is available on this subject. According to the model, Advate is cost-effective when compared to second-generation products, with a value of € 45 000/QALY, when a 16% chance of emergence of new pathogens over one year and a 6.3% cumulative transmission risk for second-generation products are assumed. Despite the fact that the scenarios used are hypothetical, the study could support decisions on the allocation of resources

Focusing on the problem of inhibitor development, an Italian group recently carried out a break-even analysis, presented as a poster (14) at the WFH 2012 congress, which assessed the cost of therapy with Advate or with a generic FVIII recombinant product "X". The study included, apart from drug costs, the possibility

that patients who develop inhibitors will start an immune tolerance regimen. The analysis also identified the inhibitor development risk threshold that would put the cost of treatment with Advate and treatment with a hypothetical FVIII recombinant product "X" at the same level.

The study is based on the following assumptions:

- on-demand treatment for 50% of patients (34.5 IU/kg) and a prophylactic regimen for the remaining 50% (32.5 IU/kg 3 times per week);
- a 0.29% probability of inhibitor development with Advate, in line with the post-marketing research (15);
- 2 years of immune tolerance treatment in case of inhibitor development;
- 5-year time horizon.

The analysis demonstrated a breakeven point of 4.44 patients with inhibitor development in the case of treatment with competitor "X", with an overall probability of 1.26%. Based on this analysis, treatment using an FVIII recombinant "X", although cheaper per unit, would be equivalent to the cost of treatment using Advate at an inhibitor development rate of 1.26% or higher.

As already described in the report published in 2011, Advate has a low inhibitor development probability for PTPs. The European Medicines Agency has identified PTPs as the ideal target group for a product's immunogenicity assessment (16, 17). The Study Group on Prophylaxis has recently summarized the results of Advate's clinical development program, revealing a total inhibitor development risk of 0.37% (95% ICs, 0.02-2.13%) (6) (Table 4).

An ongoing debate is in progress over the possibility that elimination of the B domain may be linked to an increased risk of inhibitor development. Major studies have in the past demonstrated a higher immunogenicity with BDD-FVIII than with FL-FVIII (4) and post-marketing studies are confirming these findings. In the intermediate analysis of the post-marketing surveillance study of BDD-FVIII

TABLE 4

## INHIBITOR DEVELOPMENT IN PTPS WITH ADVATE IN THE CLINICAL DEVELOPMENT PROGRAM

NO. OF PTPS TREATED IN ADVATE CLINICAL DEVELOPMENT PROGRAM	INHIBITORS OBSERVED IN ADVATE CLINICAL DEVELOPMENT PROGRAM	ESTIMATED RISK (IC <sub>95%</sub> )
270†	N=1	0.37% (0.02%– 2.13%)

†Based on combined analysis of phase II /III, III b studies

carried out in Germany and Austria, high-titer inhibitors were found in three out of 172 PTPs with an unknown or negative history of previous inhibitor development: an incidence rate of 1.7% (4, 18); two of these patients had an exposure of more than 50 days.

Parallel to this, Advate's post-marketing surveillance program found a 0.29 risk of de novo inhibitor development in 348 PTPs with more than 50 days of exposure, without a history of inhibitor development and with a FVIII  $\leq 2\%$  (15). The observed de novo inhibitor development risk was seven times higher in patients treated with BDD-FVIII than among those receiving FL-FVIII (Hazard Ratio (HR): 7.26; 95% CIs, 2.12-24.9,  $p=0.0016$ ). Moreover, the risk of high-titer inhibitor development was 11 times higher (HR 10.8; 95% CIs 2.17-53.7,  $p=0.0037$ ) (19). The overall risk finding would thus equal 2.61% for patients treated with BDD-

FVIII and 0.42% for those receiving FL-FVIII (19). These findings appear to highlight the existence of significant differences in terms of inhibitor development risk and should be taken into account when resource allocation and the promotion of post-marketing surveillance programs are discussed.

The cost difference that this data implies was the topic of a second study (20) presented at the WFH. The study was presented at the same WFH congress and, using the data described immediately above, compared costs of treatment with BDD-FVII or with FL-FVIII. The context of this study was a situation outside Italy. It compared the entire classes of FL-FVIII and BDD-FVIII drugs on the basis of an identical price per unit for both. The results show possible savings when using FL-FVIII treatment, thanks to a lower risk of inhibitor development.



## 5. Hemophilia management and the optimization of services offered by the company

With reference to disease management, we should recall that a multidisciplinary approach is crucial for proper healthcare programming and planning. As already stated in a previous report (21), adherence to prophylactic treatment may be facilitated by specific care programs. Baxter has launched a public-private partnership program for doctors, patients and the National Health Service in Italy (SSN). The program includes care services available without cost to patients:

- *Home nursing care for hemophilia patients* (Home Clinical Assistance - HCA) by specialized nurses. The goal is to teach patients or their caregivers to administer infusions autonomously. This service, provided in cooperation with the Hemophilia Center, makes patients more self-sufficient and may increase adherence to prophylactic treatment.
- *Home Rehabilitation Assistance* - HRA, provided after surgery and for the routine prevention of joint degeneration. Physiotherapy is combined with the use of the Wii Fit platform on the Nintendo console, to make the physical therapy more fun, particularly for young patients. The Company is also taking steps to supply cutting-edge medical laser equipment (High Intensity Laser Therapy, HILT) for the HRA program. The efficacy and safety of this equipment has been described (22, 23) and was recently verified in the treatment of hemophilia patients in a multi-centric study shortly to be published. Home laser therapy can be used by physiotherapists, for pain-reduction therapy and for improving joint condition.
- *Home Drug Delivery Service* - HD services, facilitating the delivery of drugs, so that patients do not have to undertake long journeys from the Hemophilia Centers
- *Online medical services* - B-nect, used to keep patients in direct contact with the care center. This enables the center to monitor the patient's therapy compliance

and to communicate messages regarding the therapy. The service uses Cisco's Web EX technology built around a specially developed application that is installed on smartphones, helping to boost patient compliance to recommended treatment regimens and therefore increase the effectiveness of therapy. B-nect is directly connected to the Italian Registry of Congenital Coagulopathies, Emoweb, making the application simple to manage and lowering the workload for care centers.

- *Home Psychological Assistance* - HPA, a service in which expert psychologists give support to patients and their relatives to increase their sense of self-esteem, help them deal better with their condition and improve adherence to the therapy regimens.
- *Sports and recreational activities with animals*. The Company also finances pet-therapy (using dogs) and equine therapy, using dogs in recreational and play programs for children and adolescents to facilitate their social integration and improve their quality of life.

If every patient that receives treatment with Advate were to make use of all the services described, we would achieve the situation shown Table 5.

The economic value of all these services totals over €31 000 per year for each patient making full use of them. This cost falls to €25 000 for adults who do not make use of recreational therapy with animals. This means that services offered with Advate make up a substantial part of the total cost of treatment (Table 6):

- 12% for adults using the minimum dosage and 8% for adults using the maximum dosage.
- 36% for children and adolescents using the minimum dosage, 23% when using the maximum dosage.

If the National Healthcare Service (SSN) contributes to treatment costs (based on cost per IU and number of IUs), patients will receive



TABLE 5

SERVICES OFFERED WITH ADVATE (PER TREATED PATIENT/YEAR)		
		EURO 2012
		COSTS MET BY BAXTER PER PATIENT/YEAR
<b>HCA</b>		€ 15 264
Average use per patient/week	3	
Average use per patient /year	144	
<b>HPA</b>		€ 3 504
Average use per patient /month	2	
Average use per patient / year	24	
<b>HRA</b>		€ 4 522
Use (including mileage reimbursement)		€ 3 600
Average use per patient / month	4	
Average use per patient/ year	48	
Annual cost WiiFIT (amortization over 4 years)		€ 65
Annual cost HIL Therapy (amortization over 4 years)		€ 857
Patients treated/ year	7	
Equine therapy		€ 3 360
Average use per patient / month	4	
Average use per patient / year	48	
Pet therapy		€ 3 360
Average use per patient / month	4	
Average use per patient / year	48	
B-nect		€ 600
<b>HD</b>		€ 1 200
<b>TOTAL</b>		€ 31 810

TABLE 6

TREATMENT COSTS AND COSTS OF SERVICES PER PATIENT/YEAR WITH ADVATE					
					EURO 2012
	COST PER UNIT IU	COST PER ADULT (MINIMUM DOSAGE)	COST PER ADULT (MAXIMUM DOSAGE)	COST PER CHILD-ADOLESCENT (MINIMUM DOSAGE)	COST PER CHILD-ADOLESCENT (MAXIMUM DOSAGE)
Treatment cost	€ 0.75	€ 204 750	€ 327 600	€ 87 750	€ 140 400
Cost of services		€ 25 090	€ 25 090	€ 31 810	€ 31 810
Cost of services on total cost (%)		12%	8%	36%	23%

Therapy with the use of horses and dogs is excluded for adults

additional services free, with an economic value ranging between 8% and 36% of therapy cost.

To conclude this section on disease management, we focus on the non-clinical aspects of Advate, such as the wide range of

available formulations (it is the only product that is also available in 1 500 IU) and the possibility of storage at room temperature for up to 6 months, holding clear practical advantages for the customization of therapy.



## 6. Conclusion

In view of the most recent findings regarding the pharmacokinetic, efficacy, safety as well as the economic and management aspects of the use of Advate, we conclude that:

- The efficacy of Advate in controlling bleeding episodes continues to be demonstrated, with a 69-70% success rate after administering a single infusion;
- Advate's hemostatic effectiveness is considered to be excellent or good in more than 90% of cases and its use in prophylactic treatment can reduce the annual bleeding rate by more than 99% compared with on-demand treatment;
- Inhibitor development remains low with a total risk of 0.37% in previously treated patients recruited in clinical studies;
- Based on the results of a study on the consumption of FL-FVIII and BDD-FVIII, carried out in the United States, a potential extrapolated saving of between 3% and 16% in costs can be obtained in Italy when using Advate compared to ReFacto AF. This figure would rise to as high as 41-57% when applying formulas published in the literature that have linked product half-life, frequency of administration and plasmatic FVIII levels;
- Recent evidence shows that the same

results can be obtained in terms of haemostatic efficacy using standard prophylaxis and prophylaxis modulated on pharmacokinetics, with a potential benefit in terms of indirect costs and quality of life thanks to a lower frequency of administration. However, further evidence is needed on this question.

- Some cost-related research suggests that differences in inhibitor development risk could have a significant impact on treatment costs, with potential savings when using products with low immunogenicity such as Advate. This evidence is supported by recent studies in which the risk of de novo inhibitor development with BDD-FVIII was estimated to be around 7 times higher than in treatment with FL-FVIII;
- Additional services offered free of charge by the Company (nursing care, physiotherapy, psychological homecare; multimedia online medical platform; home medicine delivery) could total around €31 000 for pediatric patients and around €25 000 for adults. This value, currently covered by the NHS's overall costs for managing patients with Advate, makes up 23-36% of total treatment costs for children and 8-12% of adults' total management costs.

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