

European Haemophilia Safety Surveillance System (EUHASS)- Monitoring the safety of treatments with clotting factor concentrates in Europe

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2011

- For person with severe Haemophilia in Europe
 - Supply usually not an issue
 - Costs of treatment increasing
- Risks
 - 30% risk of developing an antibody to FVIII
 - Do all products have this risk?
 - Is there a recombinant vs plasma product difference?
 - What is the risk of inhibitors in previously treated patients?
 - Is there a difference between products
- Are there any other significant adverse events?

Pharmacovigilance

- Voluntary by health professionals and patients
 - Often not used
 - Too busy, not aware of the scheme
 - Believe adverse event well known
 - Publish own series first
 - Do not report until certain
- Mandatory by manufacturers
 - Post marketing surveillance
 - Small
 - Selected patients

Pharmacovigilance Need in Haemophilia

- Large multicentre
 - to detect rare events
 - rare disease
- Simple
 - Busy clinicians
 - Multicentre
 - English not first language
- Prospective
 - Avoid recall bias
- Single scheme for all products

EUHASS

(European Haemophilia Safety Surveillance)

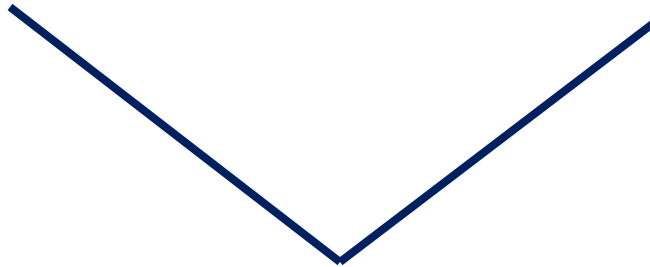
- Adverse event surveillance scheme
- European, multinational
- Sentinel centres
- Prospective
- Electronic
- English language only at present
- Started 1st Oct 2008

EAHAD

**Health
Professionals
Organisation**

EHC

**Patient
Organisation**



EUHASS

EUHASS Reportable Events

- Inhibitors
- Transfusion transmitted infections
- Allergic reactions
- Thromboses (DVT or PE, MI or Stroke)
 - Within 30 days of concentrate administration
 - No concentrate within 30 days of the event
- Malignancies
- Deaths

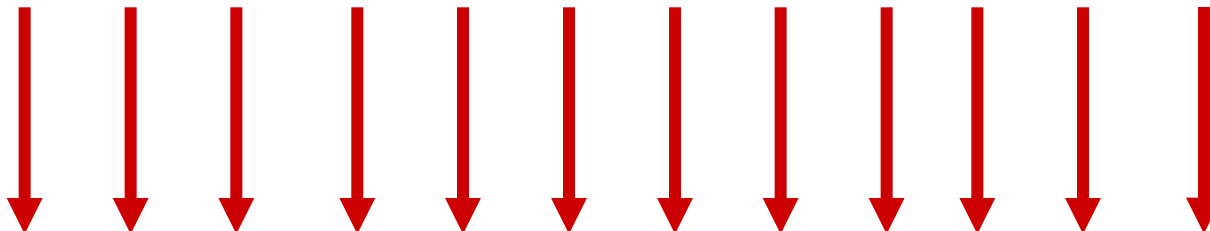
Patients for Surveillance

- Haemophilia A and B – all severities
- All VWD 2, 3 and severe type 1 (<15% RCo)
- Other rare disorders:
 - Fibrinogen defects
 - Deficiencies of II, V, VII, X, XI, XIII
 - Combined deficiencies of V+VIII, II+VII+IX+X
 - Alpha 2 anti-plasmin deficiency
- Acquired disorders excluded
- Female carriers with low FVIII/IX levels included



M3 M6 M9 M12 M15 M18 M21 M24 M27 M30 M33 M36

Adverse
Event
Data
Reporting



Cumulative
Data on
Registered &
Treated
Patients



M0

M12

M24

M36

First 2 years data

- 01.10.08-30.09.10
- 64 haemophilia centres
- 27 European countries
- 23,811 patients

Patients Under Surveillance

	Total	Severe	Concentrate treated during the year
Haemophilia A	12408	5323	6968
Haemophilia B	2622	872	1215
VWD 2	2610		369
VWD 3	376		244

	Total	Severe	Concentrate /FFP treated during the year
Afibrinogenemia	47		30
Hypofibrinogenemia	92		15
Dysfibrinogenemia	315		11
Factor II deficiency	15	9	2
Factor V	336	65	17
Factor VII	1307	286	113
Factor X	346	74	44
Factor XI	1569	230	29
Factor XIII	136	78	67
α 2 antiplasmin	4		0
Factor V+VIII	40	9	8
Factor II+VII+IX+X	19	4	4

Concentrates used

59 different products

- Recombinant
 - Advate 1934, Kogenate 1279, Helixate 855, Refacto AF 689
 - Benefix 763
- Bypass agents
 - FEIBA 157, Novoseven 292
- Others eg
 - Emoclot DI 322, Fanhdi 386, Immunate 410, Octanate 145

Adverse events reported

	Year 1	Year 2	Year 3 (up to 8 Oct)
Centres reporting	50	64	73
Allergic/Acute reactions	26	28	27
Transfusion transmitted Infections	0	0	0
Inhibitors – first occurrence	50	45	41
Inhibitors – Recurrence	5	11	6
Thrombosis within 30d of concentrate	13	15	13
Thrombosis with no concentrate in 30d	9	10	6
Malignancies	32	51	34
Deaths	48	65	75
TOTAL	183	225	202

deriving cumulative incidence from the EUHASS registry

Nr of new inhibitors*

Nr new inhibitors + Nr completed 50 ED

*Inhibitor: 2 positive tests

Inhibitors in Severe PUPS Recombinant vs Plasma FVIII (Years 1 and 2)

Concentrate	Inhibitors/PUPS	Incidence %	95% CI
Recombinant	35/138	25	18-33
Plasma	4/15	27	8-53

Inhibitors in Severe PUPS Recombinant FVIII Concentrates (Years 1 and 2)

Concentrate	Inhibitors/PUPS	Incidence %	95% CI
A	17/41	41	26-58
B	4/11	36	36-69
C	12/56	21	12-34
D	1/13	8	0-36
E	1/13	8	0-36
F	0/4	0	0-53

Inhibitors in Severe PTPs (I) (Years 1 and 2)

PTP: > 50 ED with FVIII/IX

18 in PTPs with severe haemophilia (16A, 2B)

Concentrate	Inhibitors/pt yrs	Incidence Nr/1000 ptyrs	95% CI
Haemophilia A	16/7060	2.3	1.3-3.7
Haemophilia B	2/1282	1.6	0.2-5.6

Allergic/Acute events

Event	Number
Rash / urticaria	29
Vasovagal / hypotension	8
Anaphylaxis	4
Other	13
TOTAL	54

34 of the events occurred within 10 min of product administration
38 were graded as definite or probable

Thromboses within 30 days of concentrate (Years 1 and 2)

Event	Number
Myocardial infarction	5
Angina	1
Stroke	4
Transient ischaemic attack	1
Deep Vein Thrombosis (DVT)	6
Pulmonary embolism	4
Phlebitis / port thrombosis	6
Other	1
TOTAL	28

Thrombosis in FVII deficiency

Event	Age (years)	FVII level (%)	Product	Time between last dose and thrombosis (hr)	Surgery
Stroke	50	0	Plasma VII	3	Yes
DVT	40	1	PCC 1	2	Yes
DVT	63	18	PCC2	24	No
PE	64	14	rVIIa	3	Yes
DVT	17	0	rVIIa	12	Yes
DVT *	78	0	Plasma VII	48	Yes

* Year 3 event

Malignancy (Years 1 and 2 only)

Malignancy	Number
Hepatocellular carcinoma	18
Gastrointestinal	19
Lung	11
Urogenital	14
Haematological	9
Other	12
TOTAL	83

Deaths (Years 1 and 2 only)

Cause of death	Number
Liver related	25
Intracranial haemorrhage	17
Malignancy (excluding liver)	24
Cardiac	9
Bleeding (excluding intracranial)	9
Other	29
TOTAL	113

EUHASS

European Haemophilia Safety Surveillance



Information

EUHASS is a pharmacovigilance program to monitor the safety of treatments for people with inherited bleeding disorders in Europe.

Haemophilia treatment centres report adverse events directly to the EUHASS website and regular surveillance reports are produced.

[More Information about EUHASS](#)



Haemophilia Centres

Search for Haemophilia Centres and Organisations in Europe



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Product Data

Directory of Clotting Factor Products Used in Europe



[Access the directory](#)



Participating Sites

EUHASS Systems Login
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Event Reporting

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SharePoint

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IT Systems Support



support@mdsas.com



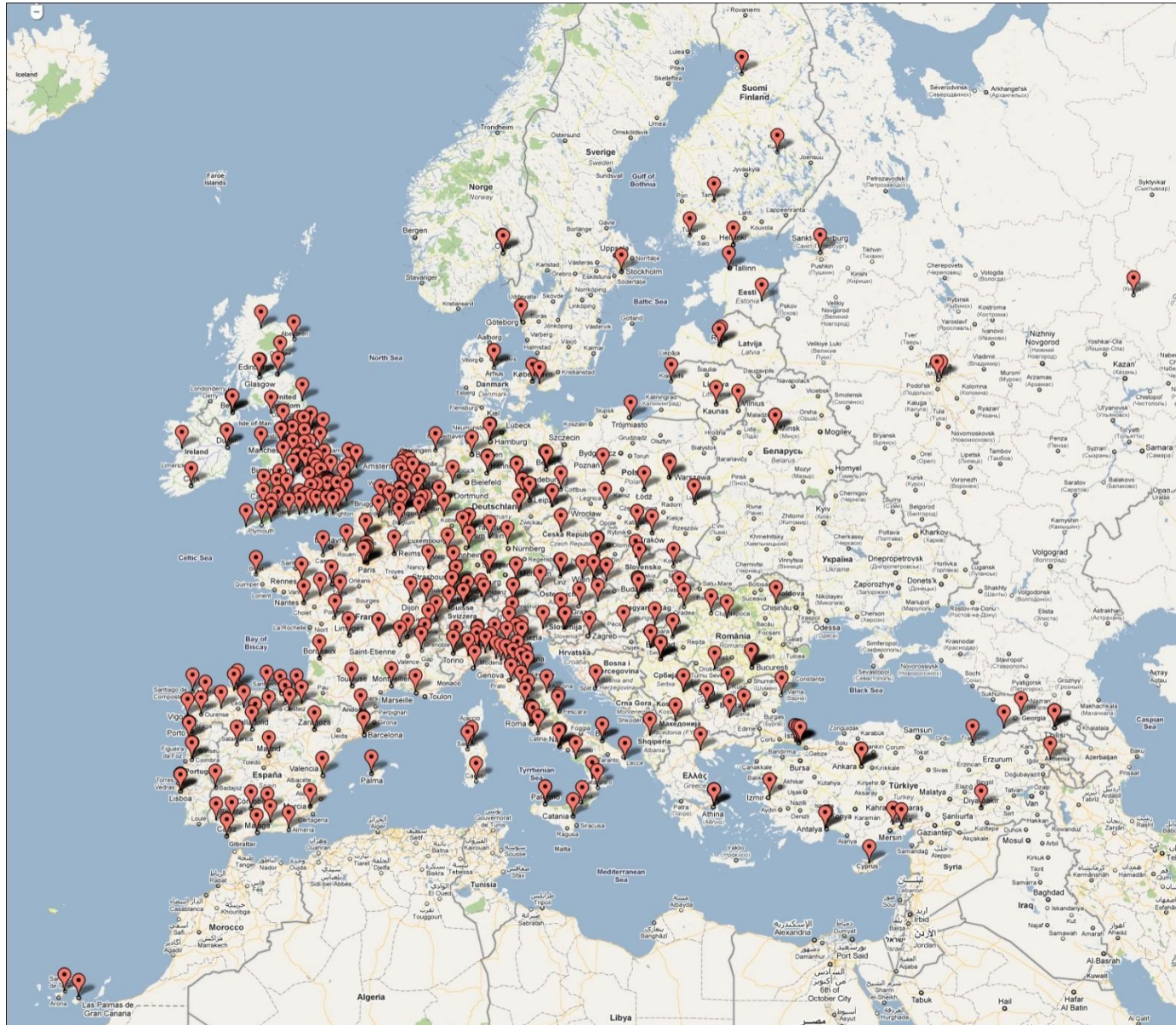
+44(0) 161 277 7920

www.euhass.org

Site visits by country (n=56) and number of visits (6,585)



European Haemophilia Centres n=420



Last Updated: 05/07/2010

Van Creveldkliniek, Dept of Hematology, University Medical Center Utrecht



Centre Address: Heidelberglaan 100, 3584 CX Utrecht ,
City: Utrecht
Country: Netherlands
Postal/Zip Code: 3584 CX



[Show on Map](#)

Centre Telephone Number: + 31 (0)88 7558450
Centre Fax Number: + 31 (0)88 7555438
Centre Email Address: yck-secretariaat@umcutrecht.nl
Centre Website: www.vancreveldkliniek.nl
Centre Director Name: Dr. Roger Schutgens

Doctors	Nurses	Physiotherapists
Dr. Evelien Mauser-Bunschoten MD PhD	Els Haan Hanny de Jonge-Harkema	Piet de Kleijn Jan Jaap van der Net
Dr. Goris Roosendaal MD PhD	Nanda de Heusden Marieke Schasfoort	
Dr. Roger Schutgens, MD PhD, Dr. Kathelijn Fischer, MD PhD, Dr. Lily Heijnen, MD, PhD	Tamara Schaefer	

Obtaining Care :

During Normal Working Hours:

There is a 24-h coverage of haemophilia care. Other contacts:
Social worker: Ruud Bos Data manager: Monique Spoor

Outside Normal Working Hours:

There is a 24-h coverage of haemophilia care. Patients can call
specialised haemophilia treaters 24/24h.

To update this information please email ehc@euhass.org

CLOSE

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Centre Address: Heidelberglaan 100, 3584 CX Utrecht ,
City: Utrecht
Country: Netherlands
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European Haemophilia Safety Surveillance

Search Haemophilia Products in Europe



Please type in a search criteria
e.g. **Brand** or **Company**

Search


Please click on desired product to show details

Results: 10 per page All

<u>Brand</u>	<u>Company</u>
Aafact®	Sanquin
Advate® = Advate rAHF PFM	Baxter Bioscience
Aimafix®	Kedrion
Alphanate®	Grifols
AlphaNine® = AlphaNine SD	Grifols
Amofil®	Sanquin OY
BeneFIX®	Wyeth Europa Ltd., an affiliate of Pfizer Ltd.
Beriate® = Beriate P	CSL Behring
Berinin® = Berinin-P = Berinin HS	CSL Behring
Beriplex® P/N = Confidex®	CSL Behring

European Haemophilia Safety Surveillance



NovoSeven® 

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Prophylaxis

Auerswald G, Morfini M Prophylaxis with recombinant factor VIIa in haemophilia patients with inhibitors. Journal of Coag Dis 2010;2:1-8
<http://www.slm-hematology.com/journal-of-coagulation-disorders/details/article/prophylaxis-with-recombinant-activated-factor-vii-in-hemophilia-patients-with-inhibitors/>

Blatny J, Kohlerova S, Zapletal O, Fiamoli V, Penka M, Smith O. Prophylaxis with recombinant factor VIIa for the management of bleeding episodes during immune tolerance treatment in a boy with severe haemophilia A and high-response inhibitors. Haemophilia 2008;14:1140-1142

Bossard D, Carrillon Y, Stieltjes N, Larbre J-P, Laurian Y, Molina V, Dirat G. Management of haemophilic arthropathy. Haemophilia 2008;14:11-19

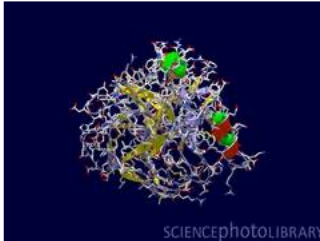
Carcao M, Chambost H, Ljung R Devising a best practice approach to prophylaxis in boys with severe haemophilia: evaluation of current treatment strategies. Haemophilia. 2010;16(s2):4-9

To update this information please email E.A.Gilman@sheffield.ac.uk

Prophylaxis with Recombinant Activated Factor VII in Hemophilia Patients with Inhibitors [Back to list](#)

Günter Auerswald and Massimo Morfini

Added: 01 February 2010



Review Article

Prophylaxis with Recombinant Activated Factor VII in Hemophilia Patients with Inhibitors

Günter Auerswald ¹ and Massimo Morfini ²

Affiliations: ¹Prof.-Hess-Kinderklinik, Bremen, Germany and ²Agency for Hemophilia, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

ABSTRACT

Treatment of bleeding episodes or during surgery in people with hemophilia A (FVIII deficiency) or hemophilia B (FIX deficiency) who have developed antibodies (inhibitors) to FVIII or FIX (especially high titer inhibitors) is difficult as a normal replacement with factor VIII or IX is not effective. rFVIIa is used to treat bleeds in patients with hemophilia who have developed such antibodies to FVIII or FIX (inhibitors, especially high titer inhibitors). Its effects on the coagulation system, however, may last for longer than pharmacokinetic data suggest. Furthermore, data supporting the concept of rFVIIa-mediated prophylaxis in hemophilia patients with inhibitors are now being published. A recently described clinical trial of prophylaxis with rFVIIa in 22 frequently bleeding hemophilia patients with inhibitors was the first to report the results of a prospective randomized study evaluating the potential benefits of a bypassing agent in such a prophylactic setting. Here we review data from this study together with other information currently available relating to the prophylactic use of rFVIIa in patients with hemophilia and inhibitors outside the surgical arena. Overall, data from more than 70 patients described in a range of publications suggest that prophylaxis with rFVIIa can decrease bleeding frequency, increase mobility, reduce pain and have other quality of life benefits in hemophilia patients with inhibitors. There are no reports of any adverse event profiles attributable to the use of rFVIIa in these patients. The prolonged prophylactic effect of rFVIIa may be explained, at least in part, by its diffusion into the extravascular space and the formation of complexes with tissue factor to facilitate thrombin generation on platelets. In addition, rFVIIa could be internalized into platelets, which subsequently increases the duration of its availability. Further research into rFVIIa prophylaxis and its mechanism of action in hemophilia patients with inhibitors is warranted.

Keywords: Hemophilia, inhibitors, prophylaxis, recombinant activated factor VII

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Other Articles

- ▶ Construction and Expression of a New Modified Coagulation FVIII cDNA In NIH3T3, CHO, and HepG2 Cell Lines
- ▶ A Case of Severe Disseminated Intravascular Coagulation During Pneumococcal Septic Shock
- ▶ Risk of Venous and Arterial Thrombosis in HIV-infected Patients: A Narrative Review
- ▶ Tissue Factor Expression by Malignant Cells Contributes to Tumor Progression
- ▶ Incidence and Risk Factors of Severe Obstetric Hemorrhage

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The Future

- EUHASS will continue
- Funding is unclear
 - Immediate from EAHAD
 - Longer term EU/Industry
- Other countries
 - Canada, South Africa, Australia
- Pharmacovigilance remains essential especially with the introduction of longer acting concentrates
- ?User level reporting
- Haemophilia community system is complementary and does not replace industry and regulatory systems

Acknowledgements

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