HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

28 May 2014

VONCENTO 250 IU / 600 IU, powder and solvent for solution for injection/infusion (solvent 5 ml)

B/1 vial (glass) of powder + 1 vial (glass) containing 5 ml of solvent (CIP: 34009 585 637 8 2)

VONCENTO 500 IU / 1200 IU, powder and solvent for solution for injection/infusion (solvent 5 ml)

B/1 vial (glass) of powder + 1 vial (glass) containing 5 ml of solvent (CIP: 34009 585 638 4 3)

VONCENTO 1000 IU / 2400 IU, powder and solvent for solution for injection/infusion (solvent 10 ml)

B/1 vial (glass) of powder + 1 vial (glass) containing 10 ml of solvent (CIP: 34009 585 639 0 4)

Applicant: CSL Behring SA

INN	Human coagulation factor VIII (FVIII) + von Willebrand factor (VWF)
ATC Code (2012)	B02BD06 (von Willebrand factor and human coagulation factor VIII in combination)
Reason for the request	**Inclusion**
List concerned	**Hospital use (French Social Security Code L.5123-2)**
Indications concerned	**“von Willebrand disease (VWD): Treatment of bleeding episodes or prevention and treatment of surgical bleeding in patients with von Willebrand disease, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.** **Haemophilia A (congenital factor VIII deficiency): Prophylaxis and treatment of bleeding in patients with haemophilia A.”**

Actual Benefit	**The AB of VONCENTO is:** - **substantial in the indication: "von Willebrand disease (VWD): Treatment of bleeding episodes or prevention and treatment of surgical bleeding in patients with von Willebrand disease, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated."** - **insufficient in the indication "Haemophilia A (congenital factor VIII deficiency): Prophylaxis and treatment of bleeding in patients with haemophilia A.**
Improvement in Actual Benefit	**VONCENTO does not provide any improvement in actual benefit (IAB V, non-existent) in the current management of von Willebrand disease.** **Haemophilia A: Not applicable**
Therapeutic use	**Von Willebrand disease: Second-line replacement therapy when desmopressin is ineffective or contraindicated.** **Haemophilia A: No established role in therapeutic use.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated (European centralised procedure): 12 August 2013
Prescribing and dispensing conditions /special status	List I Medicine requiring initial six-month hospital prescription (including blood transfusion establishments authorised to dispense medicinal products derived from blood to patients undergoing treatment). Dispensing is restricted to in-house pharmacies in healthcare establishments and to blood transfusion establishments where patients are undergoing treatment.

ATC Classification	2013	
	B	Blood and blood-forming organs
	B02	Antihaemorrhagics
	B02B	Vitamin K and other haemostatics
	B02BD	Blood coagulation factors
	B02BD06	Von Willebrand factor and coagulation factor VIII in combination

02 BACKGROUND

This is an application for inclusion on the list of products approved for use by hospitals of the proprietary medicinal product VONCENTO, a complex combining coagulation factor VIII of human origin (FVIII) and von Willebrand factor (VWF) in a FVIII/VWF ratio of 1:2.4. VONCENTO is marketed in Australia under the trade name BIOSTATE SP.[1]

In Europe, CSL Behring has for over 25 years marketed the proprietary medicinal product HAEMATE P, which differs from VONCENTO and BIOSTATE SP in the biological safety procedures employed:

- pasteurisation in the case of HAEMATE P,
- solvent/detergent treatment, dry heat-treatment and depth filtration in the case of BIOSTATE SP and VONCENTO.

HAEMATE P is available to patients in France under the terms of temporary authorisations for use by named patients [ATU nominatives in French].

[1] The first Marketing Authorisation was granted in Australia in 2000 for the proprietary medicinal product BIOSTATE RP. The manufacturing process was subsequently modified to include an additional filtration step to reduce the risk of transmission of prions, which led to a new Marketing Authorisation being granted in 2009 under the trade name BIOSTATE SP.

03 THERAPEUTIC INDICATIONS

"Von Willebrand disease (VWD): Treatment of bleeding episodes or prevention and treatment of surgical bleeding in patients with von Willebrand disease, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.

Haemophilia A (congenital factor VIII deficiency): Prophylaxis and treatment of bleeding in patients with haemophilia A."

04 DOSAGE

"**Von Willebrand disease**
It is important to calculate the dose as a function of the number of IU of VWF:RCo specified. Generally, 1 IU/kg VWF:RCo raises the plasma concentration of VWF:RCo by 0.02 IU/ml (2%). Levels of VWF:RCo of > 0.6 IU/ml (60%) and of FVIII:C of > 0.4 IU/ml (40%) should be achieved. Usually 40-80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20-40 IU FVIII:C/kg body weight (BW) are recommended to achieve satisfactory haemostasis.
An initial dose of 80 IU/kg of von Willebrand factor (VWF:RCo) may be required, especially in patients with type 3 von Willebrand disease where maintenance of optimal levels may require greater doses than in other types of von Willebrand disease.

Prevention of surgical bleeding
For prevention of excessive bleeding during or after surgery, administration should start 1-2 hours before the surgical procedure. An appropriate dose should be re-administered every 12-24 hours. The dose and duration of the treatment depend on the patient's clinical condition, the type and severity of the bleeding, and both VWF:RCo and FVIII:C levels.

As with any product containing von Willebrand factor in combination with factor VIII, prolonged treatment may cause an excessive rise in FVIII:C.
Consequently, after 24-48 hours of treatment a reduction in the administered dose and/or prolongation of the dose interval or the use of von Willebrand factor containing a low level of FVIII should be considered in order to avoid an excessive rise in FVIII:C.

Haemophilia A
It is important to calculate the dose as a function of the number of IU of FVIII:C specified. The dose and duration of the substitution therapy depend on the severity of the FVIII deficiency, on the localisation and extent of the bleeding and on the patient's clinical condition.

On-demand treatment
The calculation of the required dose of factor VIII is based on empirical data showing that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by about 2% of normal activity (in-vivo recovery 2 IU/dl). The required dose is determined using the following formula: Required units = body weight [kg] $\times$ desired increase in factor VIII [% or IU/dl] $\times$ 0.5. The amount to be administered and the frequency of administration should always be oriented to the clinical efficacy in the individual case.

In the case of the following bleeding events, the factor VIII activity should not fall below the indicated plasma activity level (in % of normal or IU/dl) during the corresponding treatment period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage / Type of surgical procedure	FVIII level required [% or IU/dl]	Frequency of doses (hours) / Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat infusion every 12-24 hours for at least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30-60	Repeat infusion every 12-24 hours for 3-4 days or more until pain and acute incapacitation are resolved.
Life-threatening bleeding	60-100	Repeat infusion every 8-24 hours until threat is resolved.
Surgery		
Minor including tooth extraction	30-60	Repeat infusion every 24 hours for at least 1 day, until healing is achieved.
Major	80-100 (pre- and postoperative)	Repeat infusion every 8-24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII activity of 30 to 60% (IU/dl).

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy through regular coagulation analyses (plasma FVIII activity) is indispensable. The response to factor VIII can vary from one patient to the next, given the observed interindividual variability in the in-vivo recovery and half life of this factor.

Prophylaxis

For long term prophylaxis in patients with severe haemophilia A, the usual dose is 20 to 40 IU factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

Previously untreated patients: The safety and efficacy of VONCENTO in previously untreated patients have not yet been established.

Special situations

- Paediatric population: Dosing in von Willebrand disease and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical efficacy in the individual case. The safety of VONCENTO in children < 12 years has not been established. No data are available.
- Older people: No dose adjustment is necessary."

05 THERAPEUTIC NEED

Von Willebrand disease

The severity of haemorrhagic signs in von Willebrand disease depends on the disease type. Type 1 (moderate quantitative forms) and type 2 (forms due to molecular variants, classified into subtypes 2A, 2B, 2M and 2N) are characterised by spontaneous bleeding or bleeding caused by an injury to the skin (prolonged bleeding after cuts and bruises) or mucous membranes (epistaxis, gingivitis, hypermenorrhoea and postpartum haemorrhage, gastrointestinal bleeding). Type 3 is used to describe severe quantitative forms.

The administration of a von Willebrand factor (VWF) concentrate is suggested when desmopressin cannot be used. The choice between administration of a pure VWF concentrate and a concentrate combining von Willebrand factor and factor VIII depends on the clinical context and on the urgency of the need to normalise haemostasis. Haemostasis is generally ensured if factor VIII coagulant (FVIII:C) levels of 0.4 IU/ml (40%) are reached. The injection of VWF alone induces a gradual recovery in FVIII:C, with peak levels achieved only after a period of 6 to 12 hours. The injection of VWF alone does not therefore allow any immediate correction in FVIII:C levels. If a rapid correction in hemostasis is required, it is therefore necessary to co-administer factor VIII in combination with VWF so as to swiftly achieve a FVIII:C level sufficient to ensure haemostasis. For the treatment and prevention of bleeding associated with surgical interventions in patients with von Willebrand disease when desmopressin is ineffective or cannot be given, either WILSTART (combination of FVIII and VWF) or WILFACTIN (VWF-based and containing FVIII in a pharmacologically inactive quantity) in combination with an FVIII concentrate may be used.

Haemophilia A

Haemophilia A is a hereditary disease caused by a sex-linked recessive gene and results from a deficiency in factor VIII. It occurs primarily in boys and is passed on by women (“carriers”) to their descendants.

The most frequent clinical manifestation is bleeding in the joints and muscles, the seriousness and frequency of which depends on the degree of deficiency. The clinical severity of haemophilia A depends on the plasma level of factor VIII:

- severe forms (< 1 IU/dl) are characterised by frequent spontaneous bleeding or abnormal bleeding following minor injuries, surgery or tooth extraction and generally appear within the first two years of life.
- moderate forms (1-5 IU/dl) are characterised by abnormal bleeding following minor injuries, surgery or tooth extraction; spontaneous bleeding is rare.
- mild forms (5-40 IU/dl) are characterised by abnormal bleeding following minor injuries, surgery or tooth extraction, but without spontaneous bleeding.

According to 2013 data from the FranceCoag network, 35% of the 5007 haemophilia A patients being monitored in France had a severe form, 15% a moderate form and 50% a mild form.

The most common forms of bleeding are intra-articular (haemarthrosis is pathognomonic for haemophilia A) and muscular haematomas. Intracranial or gastrointestinal bleeding and compressive neck or intraperitoneal haematomas require emergency treatment. Muscle haematomas may be accompanied by nerve compression; in chronic cases there is also a risk of the development of a “pseudotumour”, with erosion of the underlying bone structures. Repeated haemarthrosis in the same joint may progress to haemophilic arthropathy (destructive and irreversible cartilage and bone lesions), which can give rise to significant disability. Untreated, severe haemophilia was in the past fatal in childhood or adolescence.

A global strategy is necessary for the therapeutic management of haemophilia A. Its objective is the acute and chronic early control and/or prevention of bleeding episodes and their complications, in particular the development of haemophilic arthropathy, a complication necessitating orthopaedic or surgical treatment. For the treatment of bleeding, the prevention of bleeding associated with surgical interventions and the long-term prevention of bleeding, a proprietary medicinal product containing recombinant FVIII or FVIII of plasma origin may be used. Concomitant treatment with VWF in such patients is given only in exceptional cases.

Since the substantial reduction in the risk of infection from FVIII replacement therapy, the main complication of this treatment has been the development of (inhibitor) antibodies that inhibit its activity. The incidence of inhibitor detection in patients with haemophilia A was 11.3% in France between 1994 and 2005 and 26% in cases of severe haemophilia A.[2] Activated coagulation factor VII or activated prothrombin complex concentrates (bypassing agents) can be used as an alternative to factor VIII to treat bleeding episodes in patients who have developed inhibitors. In patients with severe haemophilia A, inhibitors may be eradicated by the administration of high-dose factor VIII concentrates. This “immune tolerance induction” therapy is normally carried out using the factor VIII that was responsible for the development of inhibitors. A number of risk factors for developing inhibitors have been identified. Some are patient-related: the risk is greater in severe haemophilia A, in the presence of certain types of genetic abnormality, in some ethnic groups, and if there is a family history of inhibitors.
Others are linked to the method of administration of factor VIII (initial treatment at an early age, intensity of treatment, method of production).
Recombinant and plasma-derived factor VIII products may also have different immunogenicity (this last-mentioned point is a matter of debate[3]).

[2] Doncarli A, Demiguel V, Ghez M, Doussin A et al. Premier état des lieux du suivi de la population hémophile en France (cohorte Francecoag, 1994-2005). Bulletin épidémiologique hebdomadaire. 2006; 39
[3] Développement des inhibiteurs et prise en charge chez les patients hémophiles traités par Facteur VIII ou IX d’origine plasmatique ou recombinante. Rapport AFSSAPS. 2006. [Development of inhibitors and management of haemophilia patients treated with plasma-derived or recombinant factor VIII or IX. AFSSAPS [French Healthcare Product Safety Agency] report. 2006.]

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The comparator medicinal products of VONCENTO are FVIII+VWF combination products or combinations of FVIII concentrate and VWF concentrate.

Proprietary medicinal products indicated in haemophilia A

NAME (INN) *Company*	Same TC* Yes/No	Indication	Date of opinion	AB	IAB	Reimbursed
FACTANE (FVIII) LFB	No	Treatment and prevention of bleeding episodes and surgical bleeding caused by factor VIII deficiency (haemophilia A) in previously treated or untreated patients in whom factor VIII inhibitors are not present. Treatment may be continued in patients who develop factor VIII inhibitors (neutralising antibodies) at levels less than 5 Bethesda units (BU) if the clinical response persists and the circulating factor VIII level increases. **Treatment of inhibitors by immune tolerance induction.** **FACTANE does not contain von Willebrand factor in sufficient quantity to be used on its own in von Willebrand disease.**	(Initial opinion: N/A) 28 March 2007 (extension of indication)	Substantial	Useful treatment option for ITI in patients who have developed inhibitors following FACTANE therapy.	Yes
OCTANATE (FVIII) Octapharma	No	Treatment and prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency). This product does not contain von Willebrand factor in a pharmacologically active quantity and is consequently not indicated in von Willebrand disease.	4 October 2006	Substantial	IAB V compared with other FVIII concentrates	Yes
ADVATE (Octocog alfa**) Baxter	No	Treatment and prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency). ADVATE does not contain von Willebrand factor in a pharmacologically active quantity and is consequently not indicated in von Willebrand disease.	16 June 2004	Substantial	IAB V compared with other recombinant FVIII products	Yes

HELIXATE NexGen (Octocog alfa) CSL Behring	No	Treatment and prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency). This product does not contain von Willebrand factor and therefore must not be used in the treatment of von Willebrand disease.	8 November 2000	Substantial		Yes
KOGENATE (Octocog alfa) Bayer	No	Treatment and prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency). This product does not contain von Willebrand factor and therefore must not be used in the treatment of von Willebrand disease.	(Initial opinion: 25 October 2000 for KOGENATE) 16 June 2004	Substantial	IAB V compared with other recombinant FVIII products	Yes
REFACTO (Moroctocog alfa**) Wyeth (Pfizer)	No	Treatment and prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency). REFACTO does not contain von Willebrand factor and therefore is not indicated in patients with von Willebrand disease.	(Initial opinion: 7 July 1999) 18 June 2003	Substantial	N/A	Yes

*Therapeutic category
**: recombinant FVIII

Proprietary medicinal products based on von Willebrand factor (VWF) indicated in von Willebrand disease:

NAME (INN) *Company*	Same TC* Yes/No	Indication	Date of opinion	AB	IAB	Reimbursed
WILSTART **(FVW+FVIII)** LFB	**Yes**	WILSTART is specifically indicated in the initial phase of treatment of von Willebrand disease when desmopressin (DDAVP) treatment is ineffective or contraindicated. **WILSTART must not be used in the treatment of haemophilia A.**	11 February 2004	Substantial	IAB V compared with the combination FACTANE + VWF LFB	Yes
WILFACTIN (VWF) LFB	No	WILFACTIN is indicated in the treatment and prevention of bleeding episodes and surgical bleeding in von Willebrand disease when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. WILFACTIN must not be used in the treatment of haemophilia A.	14 January 2004	Substantial	IAB V compared with VON WILLEBRAND FACTOR LFB	Yes

*Therapeutic category

◗ **Conclusion: The cited comparators are relevant, bearing in mind that only WILSTART is a FVIII+VWF combination product like VONCENTO**.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Marketing Authorisation	
	Yes (date)/No/ Assessment in progress	Indications and special condition(s)
Germany	Assessment in progress	Haemophilia A (treatment and prophylaxis) and von Willebrand disease (treatment and prevention of surgical bleeding)
United Kingdom	Assessment in progress	
Portugal	Assessment in progress	
Australia	Yes (2008)	
New Zealand	Yes (2008)	

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The clinical evaluation of VONCENTO is based essentially on two clinical studies, one in von Willebrand disease and the other in haemophilia A. In these two studies, an analysis of pharmacokinetic parameters was carried out to establish the bioequivalence of VONCENTO with VONCENTO SP. These studies were carried out with BIOSTATE SP (now renamed VONCENTO SP).

8.1.1 Haemophilia A

The efficacy and adverse effects of VONCENTO SP in haemophilia A were evaluated in a non-comparative phase II study (pivotal study No. CSLCT-BIO 07-47) carried out between March 2009 and March 2011 at 14 centres (7 in Poland, 3 in Bulgaria, 3 in Russia and 1 in the Republic of Macedonia). Patients with antibodies to FVIII or a history thereof (anti-FVIII inhibitors ≥ 0.6 Bethesda units) were excluded.

Results:
The results of the study have not been published. Of the 81 patients with severe haemophilia A included (with a plasma FVIII level ≤ 1%), of whom 3 were adolescents, 77 completed the study. Twenty patients underwent a total of 37 surgical procedures. The duration of follow-up was 6 months. The median injected dose of VONCENTO SP was 26.6 IU/kg (range: 14 to 40 IU/kg).

The haemostatic efficacy was rated by the investigator for each bleeding episode and was evaluated in 77 patients undergoing prophylaxis, on-demand treatment and pre-surgical prevention. It was reported for 656 of the 667 bleeding episodes that occurred in the patients included and was evaluated by the investigator as “excellent” or “good” in 96.4% of such episodes. In the prevention of surgical bleeding, the haemostatic efficacy was rated “excellent” or “good” in all cases where it was reported (in 20 procedures out of 37) after surgery, e.g. on discharge. No difference in efficacy was observed between the 3 adolescent patients and the adult patients.

8.1.2 Von Willebrand disease

The efficacy and adverse effects of VONCENTO SP in von Willebrand disease have been evaluated in a non-comparative phase II study (pivotal study No. CSLCT-BIO-08-54). This study was carried out in eastern Europe (5 centres) and Brazil (1 centre) between June 2009 and March 2011. The study included 22 patients with a severe form of the disease who had a VWF:RCo ratio < 15% on inclusion (> 5 days after any treatment) or had had a VWF:RCo ratio < 10%. Four patients, including 2 adolescents, underwent a minor surgical procedure during the study: 3 dental extraction cases and one cervical biopsy. Patients who had, or were suspected of having, FVIII or VWF inhibitors were excluded. Treatment with desmopressin acetate was unavailable, ineffective or contraindicated in these patients. The haemostatic efficacy, measured on a 4-point scale (going from “excellent” to “no effect”), was evaluated every 3 months. The number of blood transfusions required and the blood loss during surgical procedures were also measured. All analyses were exploratory in nature; no adjustment for multiple analyses was made here.

Results:
The results of the study have not been published. Twenty one (N = 21) patients received VONCENTO for a period of 12 months. The mean age of the patients was 33.6 years. Just one of these patients received treatment in the form of prophylaxis. Five patients (22.7%) had type 1 von Willebrand disease, 4 patients (18.2%) had type 2A and 13 patients (59.1%) had type 3. The mean time since diagnosis of von Willebrand disease was 22.9 years. The mean number of bleeding episodes in the 12 months prior to the study was 3.8 episodes.
The haemostatic efficacy was rated "excellent" or "good" in all patients treated on demand (n = 21) after a bleeding episode.
The haemostatic efficacy was rated by the investigator as "excellent" in 371 (91.6%) of the 405 bleeding episodes that were not surgically evaluable. It was rated as "good" in 6.7% of these episodes (27 out of 405) and "moderate" in 1.7% (7 out of 405).
The haemostatic efficacy was rated by the investigator as "excellent" in two of the dental extraction cases and "good" in the other one. In the cervical biopsy where the haemostatic efficacy was missing, the investigator rated the postoperative haemostatic efficacy as "excellent".
The efficacy results for the 4 adolescent patients included in the study did not differ from those obtained in the adult patients.

08.2 Adverse effects

8.2.1 Data from clinical studies

Haemophilia A
Four patients (4.9%) experienced 6 serious adverse events, which could have been due to the disease or to the medication in the pivotal study. The most commonly reported (> 5% of patients) were viral infections (8 patients [9.9%]), arthralgia (7 [8.6%]) and headache (5 [6.2%]).
One patient withdrew from the study on account of an increase in pre-existing FVIII inhibitors. No adverse events were observed in the adolescent patients.

Von Willebrand disease
None of the adverse events observed in the non-comparative study was evaluated as serious, except for one case of worsening of diabetes. No patients withdrew from the study on account of an adverse event. The safety profile in the four adolescent patients did not differ from that of the adult patients.

8.2.2 Pharmacovigilance data (PSURs)

International data
Following the granting of Marketing Authorisation in Australia, BIOSTATE SP (VONCENTO) has since been approved in a further 11 countries (New Zealand, Singapore, Hong Kong, Malaysia, Guatemala, El Salvador, Taiwan, Peru, Chile, Brazil and Colombia) under the name VONCENTO, ALEVIATE, human coagulation factor VIII, or TBSF human factor VIII.
The indications for haemophilia A and for von Willebrand disease have been approved in Australia, New Zealand and Brazil, whereas in the other 9 countries with Marketing Authorisation (Singapore, Hong Kong, Malaysia, Guatemala, El Salvador, Taiwan, Peru, Chile and Colombia) only the indication for haemophilia A has been approved.
Since the market launch of VONCENTO (August 2000), 1,305,190 vials had been sold up to April 2011, with approximately 2.1 adverse events per 100,000 vials and 2.5 pharmacovigilance cases reported per year.
Since August 2000 there have been 27 spontaneous reports concerning VONCENTO SP, with a total of 79 events. All of these were judged to be linked to the medicinal product and 4 were classified as "serious adverse events":

- One case of elevated liver enzymes in a patient with diagnosed hepatitis C
- One allergic reaction during administration
- One case of development of inhibitors
- One case of increase in pre-existing inhibitors.

Development of inhibitors
Since the market launch of VONCENTO SP, there have been only rare reports of the development of inhibitors (two cases). A postmarketing study was carried out in Australia between 1 July 2007 and 31 December 2007 to estimate the incidence of the development of inhibitors in patients with haemophilia A. Among the 31 patients registered with the Australian Bleeding Disorders Registry and followed up for at least 6 months, no new cases of development of inhibitors were identified, while 2 of these 31 patients had developed inhibitors prior to July 2007 and had been managed with high doses of FVIII/VWF human coagulation complex during the tolerance period (no study report available).

8.2.3 SPC data

The following adverse effects (AEs) are described in the SPC of VONCENTO: hypersensitivity or allergic reactions (up to and including anaphylactic shock), thromboembolic events, pyrexia, headache, dysgeusia and abnormal liver function test levels. The frequency of these AEs is "very rare" (fewer than one person in 10,000).

Development of neutralising antibodies
Patients with von Willebrand disease, particularly those with type 3, may develop neutralising antibodies to von Willebrand factor (inhibitors). These antibodies promote the development of anaphylactic reactions and may develop at the same time. Patients suffering anaphylactic reactions must therefore be tested for inhibitors.

Thromboembolic risk
Close monitoring of plasma FVIII:C levels is necessary. In patients with von Willebrand disease there is a risk of thromboembolic events, particularly in patients with known clinical or biological risk factors. Moreover, the administration of medicinal products containing both factor VIII and von Willebrand factor can trigger an excessive and prolonged rise in plasma FVIII:C levels likely to increase the risk of occurrence of thromboembolic events.

8.2.4 Data from temporary authorisation for use of HAEMATE P by a named patient [ATU nominative in French]

The use of HAEMATE P in France on a temporary authorisation for use by a named patient [ATU nominative in French] basis has been the subject of an observational study (2013[4]). The study aimed to evaluate the efficacy and safety of HAEMATE P in immune tolerance induction (ITI) after failure of at least one attempt at immune tolerance induction in patients with severe haemophilia A.
Nine patients at six haemophilia treatment centres were included:

- 2 patients after failure of one ITI protocol,
- 5 patients after failure of two ITI protocols including one ITI under plasma-derived factor VIII with a low FVIII/VWF ratio,
- 2 patients after failure of three ITI protocols including one ITI under plasma-derived factor VIII with a low FVIII/VWF ratio.

The patients included were judged by the investigators to have poor prognostic factors: failure of at least one attempt at ITI, inhibitor titre > 10 BU in 5 patients, median presence of inhibitors was 5.4 years (range 1.5-27.4 years). All the patients were identified as strong responders. The median duration of ITI in this publication was 32 months. A complete or partial response was obtained in 4 patients (44%): complete response in one patient and partial response in 3 patients.

[4] Rothschild C, D'Oiron R, Borel-Derlon A, Gruel Y, Navarro R, Negrier C. Use of Haemate P as immune tolerance induction in patients with severe haemophilia A who failed previous induction attempts: a multicentre observational study. Haemophilia 2013; 19: 281-286.

08.3 Summary & discussion

Haemophilia A
The efficacy of VONCENTO has been evaluated in a non-comparative study in 81 patients with severe haemophilia A previously treated with human coagulation factor VIII. In this study, the efficacy of VONCENTO in the treatment of bleeding evaluated in 77/81 patients was judged to be "excellent" in 60.4% (396 out of 656) of bleeding episodes and "good" in 36.0% (236 out of 656) of episodes.
In the prevention of bleeding during a surgical procedure, the haemostatic efficacy was judged to be excellent or good in all cases where it had been reported (20 surgical procedures) postoperatively, e.g. on discharge from hospital. Of the 37 surgical procedures carried out during the study, 12 were major and in only one case was blood loss greater than expected. Five patients in total underwent major knee surgery necessitating a blood transfusion.

Von Willebrand disease
The efficacy of VONCENTO has been evaluated in a non-comparative study in 22 patients with a severe form of the disease. The haemostatic efficacy, evaluated every 3 months, was judged by the investigator to be "excellent" or "good" in 21 patients treated on demand after a bleeding episode. The haemostatic efficacy was judged to be "excellent" in 91.6% of the 405 bleeding events that were not surgically evaluable. The haemostatic efficacy was judged to be "good" in 6.7% of these events and "moderate" in 1.7%. Four patients, including 2 adolescents, underwent a minor surgical procedure during the study: the analysis of haemostatic efficacy on discharge from hospital in the dental extraction cases was rated "excellent" in 2 of these cases and "good" in the other one. In the cervical biopsy, the investigator rated the haemostatic efficacy as "excellent".

The safety profile of VONCENTO in the two indications is expected to be the same as for other factor VIII and/or VWF concentrates. Adverse effects to be monitored particularly closely are the development of FVIII and/or VWF inhibitors, anaphylactic reaction and thrombosis. The available pharmacovigilance data, originating primarily from use of the medicinal product in Australia, have not brought to light any particular signal.

Main discussion points of these data

1) Methodological criticisms of the pivotal studies:
- They are not comparative.
- The numbers of patients included are small, particularly in von Willebrand disease.

2) Transposability
- The expected haemostatic efficacy of VONCENTO should not differ from that of WILSTART or of a combination of WILFACTIN (VWF) + FVIII concentrate. However, the available data do not allow us to compare these medicinal products with one another.
- The EMA has agreed to defer the obligation to submit the results of studies carried out with VONCENTO in patients aged between 0 and 12 years. The SPC states that the safety of VONCENTO in children under 12 years has not been established.
- The SPC of VONCENTO states that the medicinal product is subject to additional monitoring that will allow quick identification of new safety information (= medicine under additional monitoring).
- The wording of the indication for VONCENTO does not tally with the role of FVIII+VWF combinations in the management of patients with haemophilia A or von Willebrand disease (unlike that of WILSTART).

09 THERAPEUTIC USE

Haemophilia A

A global management strategy is necessary for haemophilia A patients. Replacement therapy is carried out using a recombinant factor VIII product or factor VIII of plasma origin. The first-line medicines are proprietary medicinal products based on FVIII. WILSTART must not be used in the treatment of haemophilia A. The role of VONCENTO in the treatment of haemophilia A appears very limited.

The FVIII/VWF complex comprises two substances (factor VIII and von Willebrand factor) with different physiological functions. After infusion in a patient with haemophilia A, the factor VIII binds to the von Willebrand factor in the bloodstream. Some patients who have developed inhibitors may benefit from concomitant administration of FVIII and VWF. The most effective method, and the method most commonly used to eradicate inhibitors, is immune tolerance induction (ITI). The continued administration of high-dose FVIII for a period of several months or even years induces specific immune tolerance.

According to the expert guidelines,[5] the administration of a concentrate combining FVIII and VWF as second-line treatment after failure of at least one initial ITI may be considered in haemophilia A patients.

The data (low level of evidence) suggest that the presence of von Willebrand factor in factor VIII concentrates of plasma origin may reduce the risk of inhibitors developing in patients undergoing primary prophylaxis compared with those treated with recombinant factors.[6,7,8]

According to a pooled analysis of data obtained in 32 children and 9 adults treated with HAEMATE P,[9] complete ITI was observed in all patients with good prognostic factors, weak responders and strong responders alike, and in 73% of patients who were strong responders and had poor prognostic factors. No cases of recurrence of inhibitors were reported during 12 years of follow-up of the patients. In four patients who did not respond to an ITI protocol carried out using a highly purified concentrate of plasma origin, the switch to a plasma derivative with a high VWF/FVIII ratio (HAEMATE P) successfully achieved ITI.[10] Experience from two German centres (Bonn and Frankfurt) suggests there is a link between the ITI percent success rate and the type of concentrate used. The use of a concentrate with a high VWF/FVIII ratio (HAEMATE P) resulted in elimination of inhibitors in 90% of patients after a median period of 4 months, whereas this percentage was significantly lower after use of FVIII free of VWF.[11] These favourable results are not, however, confirmed by data from a US ITI registry.[12] Some studies have, moreover, demonstrated the feasibility of ITI using recombinant FVIII or plasma-derived concentrates that are

[5] Benson G, Auerswald G, Elezovic I, Lambert T, Ljung R et al. Immune tolerance induction in patients with severe hemophilia with inhibitors: expert panel views and recommendations for clinical practice. Eur J Haematol. 2012; 88(5): 371-9.

[6] Goudemand J. Inhibitor development in haemophilia A: the role of von Willebrand factor/factor VIII concentrates. Haemophilia 2007; 13 (suppl.5): 47-51.

[7] Kallas A. et al. von Willebrand factor in factor VIII concentrates protects against neutralization by factor VIII antibodies of haemophilia A patients. Haemophilia 2001; 7: 375-380.

[8] Gensana M. et al. Influence of von Willebrand factor on the reactivity of human factor VIII inhibitors with factor VIII. Haemophilia 2001; 7: 369-374.

[9] Escuriola Ettingshausen C, Kreutz W. A review of immune tolerance induction with HAEMATE® P in haemophilia A. Haemophilia 2013 Oct 24. doi: 10.1111/hae.12288

[10] Kreuz W, Mentzer D, Auerswald G, Becker S, Joseph-Steiner J. Successful immune tolerance therapy of F VIII-inhibitor in children after changing from high to intermediate purity F VIII concentrate (abstr). Ann Hematol 1996; 72: A85.

[11] Kreuz W, Escuriola-Ettingshausen C, Auerswald G et al. Immune tolerance induction (ITI) in haemophilia A with inhibitors: the choice of concentrate affecting success. Haematologica 2001; 86 (Suppl. 4): 16-20.

[12] DiMichele DM. et al. Analysis of the North American Immune Tolerance Registry (NAITR) 1993-1997: current practice implications. ISTH Factor VIII/IX Subcommittee Members. Vox Sang 1999; 77 (Suppl. 1): 31-32.

highly purified by chromatography and totally free of VWF.[13,14] A study with HAEMATE P (RES.I.ST. study = Rescue Immunotolerance Study) that is seeking a definitive answer to this question is currently underway.

All in all, the role of VONCENTO in haemophilia A is not established:

- There is no role for VONCENTO in France for this concentrate of plasma origin that is richer in VWF than in FVIII, as five highly purified FVIII concentrates are already available.
- The company cites the benefit of VONCENTO as a second- or third-line option in ITI for patients who do not respond to recombinant factor VIII or plasma-derived factor VIII with a lower VWF content. This is not documented anywhere in the clinical dossier. The rationale is based essentially on results with HAEMATE P (FVIII and Willebrand concentrates in equal proportions) in these indications, in the form of an international registry with a small patient population and around ten documented cases in France. The benefit of this medicinal product in failed ITI is not well documented.

Von Willebrand disease

Replacement therapy with von Willebrand factor (VWF) is used in the treatment of patients with von Willebrand disease when desmopressin is ineffective or contraindicated, i.e. primarily in cases of type 2 or 3 von Willebrand disease, and in some patients with type 1 von Willebrand disease. The administration of von Willebrand factor allows the correction of haemostatic disturbances in patients deficient in von Willebrand factor (VWF), primarily through subsequent correction of the associated deficiency in factor VIII. When administered intravenously, von Willebrand factor binds to endogenous factor VIII, stabilising it and thereby averting its rapid breakdown. The administration of pure von Willebrand factor (product containing von Willebrand factor, but with a low factor VIII content) normalises FVIII:C levels within a short time after the first injection. **The administration of a product containing a FVIII+VWF concentrate allows normalisation of FVIII:C levels immediately after the first infusion.**
In practice, diagnostic tests therefore include the performance of a desmopressin test to determine whether the patient is a responder. Like WILSTART, VONCENTO must be used only in patients in whom desmopressin is ineffective or contraindicated. There is no clinical rationale for any distinction between VONCENTO and WILSTART, given that the Marketing Authorisation of WILSTART states that it is specifically indicated for the initiation of von Willebrand factor replacement therapy in patients in whom plasma factor VIII levels are considered inadequate (French test: initial factor VIII:C level < 20 IU/dl).

If the expected plasma activity levels for factor VIII or VWF are not achieved after administration of replacement factor, if bleeding is not controlled despite administration of an appropriate dose, or in the event of an anaphylactic reaction, the patient must be tested for inhibitors of the replacement factor (FVIII, VWF).

[13] Battle J, Lopez MF, Brackmann HH, Gaillard S, Goudemand J, Humbert J, De Moerloose P et al. Induction of immune tolerance with recombinant factor VIII in haemophilia A patients with inhibitors. Haemophilia 1999; 5: 431-435.
[14] Rocino A. et al. Successful immune tolerance treatment with monoclonal or recombinant factor VIII concentrates in high responding inhibitor patients. Vox Sang 1999; 77 (Suppl. 1): 65-69.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

Haemophilia A

◗ Haemophilia A causes bleeding, which can be serious and life-threatening.
◗ VONCENTO is a replacement therapy intended for curative and preventive use.
◗ The efficacy/adverse effects ratio for VONCENTO is not established in the management of haemophilia A patients who have developed inhibitors.
◗ The role of VONCENTO in this indication has yet to be established.
◗ There are alternative drug therapies, including in patients in whom inhibitors have developed.
◗ Public health benefit: it is not expected that VONCENTO will benefit public health, given its lack of a role in the therapeutic strategy for haemophilia A.

Taking account of these points, the Committee considers that the actual benefit of VONCENTO is insufficient in the prophylaxis and treatment of bleeding in patients with haemophilia A.

The Committee does not recommend inclusion on the list of medicines approved for hospital use in this indication and at the dosages in the Marketing Authorisation.

Von Willebrand disease*:*

◗ Von Willebrand disease causes bleeding, which can be serious and life-threatening.
◗ VONCENTO is a replacement therapy intended for curative and preventive use.
◗ The efficacy/adverse effects ratio in this indication is high.

◗ Public health benefit:
Despite the seriousness of von Willebrand disease, the burden due to this rare disease can be considered low.
Improving the management of rare diseases is a public health need that is an established priority (a priority of the National Technical Group for Defining Public Health Objectives and the National Rare Diseases Plan 2011-2014).
The available data do not allow us to assess the direct impact of VONCENTO on morbidity and mortality compared with that of other existing treatments or to predict whether VONCENTO will be better able to meet the public health need identified.
Consequently, in the current state of knowledge and in view of the fact that other therapies are already available, it is not expected that VONCENTO will have any impact on public health.

◗ VONCENTO is a second-line therapy when desmopressin is contraindicated or ineffective.
◗ There are alternative drug therapies in patients requiring combined administration of FVIII+VWF: WILSART or WILFACTIN + recombinant or plasma-derived FVIII concentrate.

Taking account of these points, the Committee considers that the actual benefit of VONCENTO is substantial in the treatment of bleeding episodes or prevention and treatment of surgical bleeding in patients with von Willebrand disease, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated and when administration of FVIII+VWF is required.

The Committee recommends inclusion on the list of medicines approved for hospital use in this indication and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

Haemophilia A:
Not applicable.

Von Willebrand disease:
VONCENTO provides no improvement in actual benefit (IAB V, non-existent) in the treatment of bleeding episodes or prevention and treatment of surgical bleeding in patients with von Willebrand disease, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.

010.3 Target population

Haemophilia A:
Not applicable.

Von Willebrand disease:
The target population of VONCENTO is defined as patients with von Willebrand disease in whom treatment with desmopressin is ineffective or contraindicated for the prevention or treatment of surgical bleeding and who require combined administration of factor VIII and von Willebrand factor.

Estimation of the target population
The prevalence of von Willebrand disease varies from 0.1 to 1% depending on the study, but the number of patients requiring specific treatment has been estimated at between 1/50,000 and 1/8500. In France in 2013, between 1311 and 7716 patients out of 65,586,000 citizens had a symptomatic form of von Willebrand disease. VWF deficiency can be quantitative (type 1 or type 3) or qualitative (2A, 2B, 2M, 2N):

- type 1 (least severe form, with partial deficiency in VWF and sometimes in FVIII too): 70-80% of patients;
- type 2 (decrease in VWF and sometimes FVIII too): 20% of patients, classified into subtypes (2A: 30%; 2B: 28%; 2M: 8%; 2N: 34%);
- type 3 (most serious form, with total deficiency in VWF and serious deficiency in FVIII too): 1-3% of patients.

The number of patients who are unable to be treated with desmopressin is estimated as follows:

- ineffective in 10% of patients with type 1 and in 2/3 of patients with types 2A, 2M and 2N;
- contraindicated or ineffective in all patients with types 2B and 3.

Based on this information, the number of patients with the severe form of von Willebrand disease who are unable to be treated with desmopressin is between 360 and 2200.

The target population of WILFACTIN and WILSTART was estimated by the Transparency Committee in 2004 as between 600 and 1600 patients. This estimate appears to be confirmed by recent data from the FranceCoag network. The number of individuals with von Willebrand disease currently enrolled in the FranceCoag cohort is 1548 patients.[15] According to the same source, 76% of the patients enrolled at the end of 2010, who had haemophilia, von Willebrand disease or another hereditary coagulation protein deficit, had undergone replacement therapy with a coagulation factor concentrate at least once. Applying this frequency to the number of patients enrolled in the cohort in 2013, approximately 1200 patients with von Willebrand disease are likely to receive replacement therapy. Moreover, although 4% of the patients in the von Willebrand cohort had received prophylactic treatment in 2013, patients receiving long-term prophylaxis are not counted as having been treated with a combined FVIII+VWF concentrate.

The number of patients likely to be treated with a combined FVIII+VWF concentrate in situations requiring an immediate correction of haemostasis will currently be around 1150 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration. Its use is likely to simplify prescriptions and the management of medicine stocks for patients being treated at home. The availability of three presentations (600 IU VWF, 1200 IU VWF and 2400 IU VWF) is likely to make dose adjustment easier compared with WILFACTIN (only one dosage = 1000 IU).

[15] FranceCoag network. National statistics. von Willebrand disease. http://www.francecoag.org/SiteWebPublic/public/stats/stats_page.jsp?stat4=on