HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

10 March 2010

**FIBROGAMMIN 62.5 U/ml, powder and solvent for injection or infusion**
**B/1 Powder in vial + 4 ml of solvent in ampoule (CIP: 575 416-9)**
**B/1 Powder in vial + 20 ml of solvent in ampoule (CIP: 575 417-5)**

**Applicant: CSL BEHRING SA**

Coagulation factor XIII

ATC code: B02BD07

List I
Medicinal product for initial hospital prescription

Registered on the French "rétrocession" [dispensing of drugs to outpatients by hospital pharmacies] list

Date of Marketing Authorisation (national procedure): 28/09/2009
Temporary Authorisation for Use status [French: "ATU"] prior to approval of marketing authorisation. Since 1996, temporary authorisation for use by named patients has been granted in 31 cases for patients with congenital factor XIII deficiency.

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

Coagulation factor XIII.

## 1.2. Originality

FIBROGAMMIN is the only (plasma-based) factor XIII currently available. It is an old medicinal product (1993).
It has been supplied under the temporary authorisation for use by named patient scheme in France since 1996, and all patients are treated with this medicinal product. The granting of marketing authorisation in France therefore formalises well-established practice in the use of this medicinal product for this condition.

## 1.3. Indication

"FIBROGAMMIN is indicated in the treatment and prophylaxis of haemorrhage and wound healing disorders in patients suffering from congenital factor XIII deficiency".

## 1.4. Dosage

"Treatment with FIBROGAMMIN must be managed by a doctor specialised in constitutional haemorrhagic diseases.

**Dosage**

1 ml is equivalent to 62.5 U and 1.6 ml is equivalent to 100 U.

Important

The amount to be administered and the frequency of administration should always be oriented towards clinical efficacy in the individual case.

*Prophylaxis of haemorrhages:*

10 U per kg body weight approximately once a month. The interval is to be shortened if spontaneous haemorrhages develop.

*Before surgical operations:*

Up to 35 U per kg body weight, repeated if necessary in order to attain an appropriate factor XIII level. Efficacy should be maintained by repeated injections until the wound has healed completely.

*Treatment of haemorrhages:*

10-20 U per kg body weight daily for severe haemorrhages and extensive haematomas until bleeding has stopped.

Due to the different pathogeneses of factor XIII deficiencies, the data available on half-lives differs considerably. Thus, monitoring the increase in factor XIII activity by means of factor XIII assay is recommended. In the case of major surgery and severe haemorrhages, the aim is to obtain normal factor XIII values.

**Mode of administration**

Reconstitute the product as described in the "Reconstitution" section of the marketing authorisation. The preparation should be warmed to room or body temperature before administration. Slowly inject or infuse intravenously at a rate which the patient finds comfortable. The injection or infusion rate should not exceed 4 ml per minute.

Observe the patient for any immediate reaction. If any reaction apparently linked to administration of FIBROGAMMIN takes place, the rate of infusion should be decreased or the infusion stopped, as required by the clinical condition of the patient."

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification

| | |
|---|---|
| B: | Blood and blood forming organs |
| B02: | Antihaemorrhagics |
| B02B: | Vitamin K and other haemostatics |
| B02BD: | Blood coagulation factors |
| B02BD07: | Coagulation factor XIII |

### 2.2. Medicines in the same therapeutic category

There are no similar medicines.

### 2.3. Treatments with a similar therapeutic aim

Fresh frozen plasma (FFP).

## 3 ANALYSIS OF AVAILABLE DATA

The dossier includes:

- a pharmacokinetics study (study BI 71.023/7MN-101PK)
- an observational study (study CE1232 / 0-5001) investigating the safety of use, tolerance and efficacy of factor XIII concentrate (FIBROGAMMIN). This study was carried out by the pharmaceutical company in 15 centres in France between March 1999 and July 2001.

### 3.1. Efficacy

- **Observational study (CE1232 / 0-5001)**

Objectives

The objectives of this study were to assess the efficacy, pharmacokinetics and safety of use of FIBROGAMMIN.

Primary inclusion criteria:

Patients of any age with congenital factor XIII deficiency who had been treated only with FIBROGAMMIN were eligible for the study.

**Treatments**

Patients were treated with FIBROGAMMIN according to different protocols (prophylaxis or treatment on request) and at the following dosages:

- Prophylactic treatment of haemorrhages: 10 U/kg every four weeks. The interval can be shortened in the event of spontaneous haemorrhages.
- Pre-surgical treatment: up to 35 U/kg just before surgery, approximately 10 U/kg per day in the five days after the operation or until the wound has completely healed.
- Treatment of severe haemorrhages and extensive haematomas: 10 to 20 U/kg daily until the bleeding has completely stopped.

The doses administered and the frequency of administration were adjusted according to each patient's clinical response.

Primary efficacy endpoints:
Efficacy as coagulation factor replacement was assessed by:

- Plasma factor XIII activity measured 30 minutes (± 5 minutes) after the end of infusion.
  - Response (U/ml/U/kg) = increase in factor XIII activity (U/ml) / dose (U/kg)
  - Recovery (%) = increase in factor XIII activity (U/ml) / dose (U) x 100

    Plasma volume (mL)*

* Plasma volume is defined by: 70 x weight (kg) x (100 - haematocrit (%)) / 100

- Incidence of haemorrhagic episodes.

Results

- *Patient cohort characteristics*

The patients taking part (N=19, 14 male and 5 female) were aged from less than one month to 47 years, and were suffering from congenital factor XIII deficiency. They had all been given FIBROGAMMIN at least once.
The residual factor XIII plasma activity levels, measured at the start of the study, ranged from 0.2 to 6.0%[1] (average value 1%). A total of 12 haemorrhagic episodes had been reported for eight patients in the year prior to the inclusion visit. The types of haemorrhage most frequently reported were soft tissue haemorrhages (four times in three patients).
Patients were monitored for at least 357 days, and none of the patients withdrew from treatment prematurely.

- *Increase in plasma factor XIII activity*

An increase in factor XIII activity was observed in 10 of the 19 patients taking part in the study. The average response was 1.88%/U/kg and the average recovery was 83.6%.

- *Incidence of haemorrhagic episodes*

Ten of the 19 patients were reported to have experienced haemorrhages (Table 1). The haemorrhagic episodes most frequently reported affected the soft tissues and the muscles (five cases).

**Table 1: Incidence of haemorrhagic episodes**

| Haemorrhagic episodes by type | Number of patients experiencing a haemorrhagic episode | Number of patients not experiencing a haemorrhagic episode |
|---|---|---|
| Joints | 2 | 17 |
| Soft tissues | 3 | 16 |
| Muscles | 3 | 16 |
| Gastrointestinal | 0 | 19 |
| Urogenital | 2 | 17 |
| Central nervous system | 1 | 18 |
| Other | 3 | 16 |
| **Total** | **10** | **9** |

Haemostatic efficacy was analysed according to the type of treatment. The therapeutic mode chosen was recorded for 17 of the 19 patients:

- Among the 12 patients receiving prophylactic treatment, haemorrhagic incidents were reported for four patients (at least 19 haemorrhagic events in total). One of these four patients was described as a "good responder" to treatment, but no opinion was recorded as to the efficacy of the treatment for the three other patients.
- Eight haemorrhagic events were recorded among the three patients who were treated "on request". Two of these patients were described as having an excellent response to treatment, while no information was recorded for the third patient.

[1] The normal figure is between 1 and 5%

- Sixteen haemorrhagic events were recorded for the four patients on a mixed treatment regimen (prophylaxis alternating with treatment on request). Response to treatment was described as excellent for one patient, good for one patient, moderate for one patient and no information was available for one patient.

### 3.2. Adverse effects

No death or serious adverse event was reported during this study. Only two cases of adverse events were reported:

- One case of migraine lasting one day. The investigators described this as of moderate intensity and not attributable to the treatment.
- One case of allergic reaction (urticaria or similar), of moderate intensity, which resolved spontaneously in 24 hours. This patient was on a prophylaxis regimen and did not develop any reaction during subsequent infusions.

None of the patients undergoing treatment developed anti-factor XIII antibodies.

One patient developed parvovirus B19 seroconversion after previously testing negative. However, the investigators were unable to determine the exact cause of the seroconversion. This patient was not reported as having any disease or allergic reaction.

### 3.3. Conclusion

The efficacy of factor XIII concentrate (FIBROGAMMIN) in the treatment and prevention of haemorrhages in patients suffering from congenital factor XIII deficiency has been assessed in a prospective observational study carried out on 19 patients (14 male/5 female, aged from under one month to 47 years). The residual factor XIII plasma activity levels, measured at the start of the study, ranged from 0.2 to 6.0% **(**average value 1%)[2].
Patients were treated with FIBROGAMMIN according to various protocols (prophylaxis n = 12, treatment on request n = 3, alternation between prophylaxis and treatment on request n = 4) and were monitored for at least 357 days. None of the patients withdrew from treatment prematurely.

An increase in factor XIII activity was observed in 10 of the 19 patients taking part in the study. The average response was 1.88%/IU/kg.

Ten of the nineteen patients taking part were reported to have experienced haemorrhagic episodes. These most commonly affected the soft tissues and the muscles (five cases). Eight of the twelve patients on a prophylaxis regimen did not experience any haemorrhagic incident.

However, the amount of data available from this study is insufficient to demonstrate the impact of FIBROGAMMIN on reducing haemorrhagic episodes. The haemorrhagic risk to which various groups are exposed varies, and not enough attention was paid to this factor in this study.

Clinical experience reported regarding the use of this medicinal product has not given rise to any major concerns regarding safety in use.

[2] The normal figure is between 1 and 5%

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Factor XIII deficiency is a very rare congenital disease characterised by potentially life-threatening bleeding.

FIBROGAMMIN is a first-line medicinal product for curative or preventive use.
Its efficacy/adverse effects ratio is high.

Fresh frozen plasma is the only alternative treatment.

Public health benefit

Congenital factor XIII deficiency is a serious hereditary coagulation disorder which is a minor public health burden because it is so rare.

Improving the management of this coagulation disorder is a public health need that is part of an established priority (National Rare Diseases Plan).

This medicinal product is expected to have an impact in terms of morbidity, mortality and quality of life (including education and social life) for these patients in the light of the limited amount of clinical data available (observational study of factor XIII activity and the incidence of haemorrhage among 19 patients), but also taking into account of the advantages which the medicinal product FIBROGAMMIN offers over fresh frozen plasma (large amount of factor XIII in a smaller volume, better protection against viruses, ease of use since patients can inject themselves at home). However, the size of the population means that this impact can only be very small.

Consequently, and given the small size of the population affected, there is unlikely to be any public health benefit from putting the medicinal product FIBROGAMMIN on the market, since it has been available for use in this indication in France under the temporary authorisation for use scheme for many years.

The actual benefit provided by FIBROGAMMIN is substantial.

### 4.2. Improvement in actual benefit (IAB)

Given the absence of any alternative treatment validated by marketing authorisation, and on the basis of clinical experience reported as to the benefits of this medicinal product, the Committee is of the opinion that FIBROGAMMIN offers a major improvement in actual benefit (level I) in the management of patients suffering from congenital factor XIII deficiency.

### 4.3. Therapeutic use

Congenital factor XIII deficiency is a hereditary coagulation disorder caused by a decline in the level and activity of factor XIII, characterised by a tendency to haemorrhage, high levels of miscarriage, and poor wound healing. The disease affects both men and women. It can develop at any age, but is normally diagnosed in childhood. In 80% of cases it is revealed by umbilical cord haemorrhage. The other haemorrhagic manifestations are intracranial haemorrhage (25-30%), soft tissue bleeding, ecchymosis, haemarthrosis (20%), and repeated miscarriage. Post-traumatic or post-surgical haemorrhages do not occur immediately (onset after 12 to 36 hours). Diagnosis is based on a quantitative measurement of factor XIII activity or factor XIII antigen.

Haemorrhagic episodes are treated with factor XIII concentrate or, if this is not available, with fresh frozen plasma. Prophylactic treatment with factor XIII concentrate can be given to prevent the most frequent and most serious forms of haemorrhage, such as intracranial haemorrhage.

Role of FIBROGAMMIN in treatment strategy

FIBROGAMMIN is the only factor XIII concentrate currently available in the world. The only alternative treatment is fresh frozen plasma (FFP). This presents the drawbacks of very long injection times and the risk of volaemic overload, viral transmission and allergic reactions (as the product contains many other substances in addition to factor XIII).
FIBROGAMMIN has the advantage of being a more concentrated form of factor XIII (62.5 U/ml compared to 1 U/ml in FFP), which means that patients can receive a large amount of factor XIII in a smaller volume of product. Pasteurisation increases protection against viruses, and PSURs have also indicated that the concentrate is well tolerated.
Patients in France who have been identified as suffering from a severe constitutional factor XIII deficiency are all treated with FIBROGAMMIN, except in exceptional emergency situations. FIBROGAMMIN has been available to named patients under the temporary authorisation of use scheme since 1996. Prescriptions can be renewed every six months. Consequently, patients have already been benefiting from this treatment for several years.

### 4.4. Target population

The prevalence of congenital factor XIII deficiency is estimated at 0.4/1,000,000 individuals[3].
However, there are no official statistics on the number of people in France suffering from severe factor XIII deficiency.
Data produced by the Réseau FranceCoag in 2005[4] on the basis of research carried out by InVS showed that 16 patients had factor XIII deficiency (median age at diagnosis in years: 0.09 [min 0 - max 26.6]); however, the methodology used to make up the cohort does not allow any conclusions to be drawn as to how exhaustive it is[5].

The pharmaceutical company states that 34 temporary authorisations for use for named patients had been issued by AFSSAPS, 31 of which were for the indication in the marketing authorisation.

On the basis of this information, the target population could be estimated at around thirty patients.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and at the dosage in the marketing authorisation.

[3] Orphanet report: Prevalence of rare diseases, November 2009, no. 1.
[4] French cohort of patients suffering from haemorrhagic diseases caused by hereditary coagulation protein deficiencies Réseau FranceCoag - descriptive data produced in 2005
[5] Recruitment was based purely on a single source of information (voluntary reports by doctors).