HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 March 2011

RIASTAP 1g, powder for solution for injection / infusion
B/1 glass vial (CIP code: 494 884-2)

Applicant: CLS BEHRING SA

Human fibrinogen
ATC code (2011): B02BB01

List I
Medicine for hospital prescription only

Date of Marketing Authorisation: 28 October 2010 (mutual recognition procedure)

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

Human fibrinogen

1.2. Indication

"Treatment of bleeding in patients with congenital hypo-, or afibrinogenaemia with bleeding tendency".

1.3. Dosage and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.

The dosage and duration of the substitution therapy depend on the severity of the disorder, location and extent of bleeding and the patient's clinical condition.
The (functional) fibrinogen concentration should be determined in order to calculate individual dosage. The amount and frequency of administration should be determined on an individual patient basis by regular measurement of plasma fibrinogen concentration and continuous monitoring of the clinical condition of the patient and other replacement therapies used.
Normal plasma fibrinogen concentration is in the range of 1.5 – 4.5 g/L. The critical plasma fibrinogen concentration below which haemorrhages may occur is approximately 0.5 – 1.0 g/L. In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.
Initial dose:
If the patient's fibrinogen concentration is not known, the recommended dose is 70 mg per kg of body weight (bw) administered intravenously.
Subsequent dose:
The target concentration (1 g/L) for minor events (e.g. epistaxis, intramuscular bleeding or menorrhagia) should be maintained for at least three days. The target concentration (1.5 g/L) for major events (e.g. head trauma or intracranial haemorrhage) should be maintained for seven days.

$$\text{Dose of fibrinogen (mg/kg body weight)} = \frac{[\text{Target concentration (g/L)} - \text{Measured concentration (g/L)}]}{0.017 \text{ (g/L per mg/kg body weight)}}$$

Dosage for neonates, infants and children:
Limited data from clinical studies regarding the dosage of RIASTAP in children are available. Resulting from these studies, as well as from long lasting clinical experience with fibrinogen products, dosage recommendations in the treatment of children are the same as for adults.

Method and route of administration

Intravenous infusion or injection.
RIASTAP should be reconstituted according to the instructions given in section 6.6 of the SPC, special precautions for disposal and other handling. The reconstituted solution should be warmed to room or body temperature before administration, then injected or infused slowly at a rate which the patient finds comfortable. The injection or infusion rate should not exceed approx. 5 mL per minute.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

B : Blood and Blood Forming Organs
B02 : Antihemorrhagics
B02B : Vitamin K and Other Haemostatics
B02BB : Fibrinogen
B02BB01 : Fibrinogen, human

2.2. Medicines in the same therapeutic category

2.2.1 Comparator medicines

CLOTTAFACT (fibrinogen, human)

2.2.2 Medicines not strictly comparable

Not applicable.

2.3. Medicines with a similar therapeutic aim

Fresh frozen plasma. Fresh frozen plasma is not a medicine.

3. ANALYSIS OF AVAILABLE DATA

The company has submitted reports for six studies in which RIASTAP appears under the name of HAEMOCOMPLETTAN P, i.e. one single-dose pharmacokinetics and efficacy study, one retrospective efficacy and tolerance study, one retrospective survey to collect information on congenital fibrinogen deficiency and types of treatments used, one single-dose pharmacokinetics study (of which only the section on tolerance was used), one viral tolerance study, and one prospective observational study concerning off-label use (of which only the section on tolerance was used).

3.1. Efficacy

3.1.1 Study BI3023 2001 (2008)

The pharmacokinetics section of this study was not used.

Aim:
To study the haemostatic efficacy of a single dose of HAEMOCOMPLETTAN P using a surrogate endpoint in patients with congenital fibrinogen deficiency.

Method
Non-comparative study

Primary endpoint:
- Change in maximum clot firmness (MCF) as measured by thromboelastometry before and one hour after administration of HAEMOCOMPLETTAN P. The scientific advice of the CHMP was that MCF seemed to be an acceptable surrogate endpoint for haemostatic efficacy. The SPC for RIASTAP states in section 5.1 (pharmacodynamic properties), "Haemostatic efficacy in acute bleeding episodes, and its correlation with MCF, are being verified in a post-marketing study".

Treatment: a single dose of HAEMOCOMPLETTAN P, 70 mg/kg, administered by intravenous infusion.

Main inclusion criteria:
- Subjects aged at least 6 years
- confirmed congenital afibrinogenaemia
- no active bleeding events
- plasma fibrinogen activity and antigen undetectable on inclusion (<20 mg/dL).

Statistical methods:

Bilateral t-test for paired data, assuming a normal distribution of change in MCF. This type of test is not appropriate for a small sample.

Results
A total of 15 subjects were included. Mean age was 29.5 ± 15.9 years (8-61 years); 4 patients were aged under 16 years.

Results for change in maximum clot firmness are given in*Table1*

Table 1: maximum clot firmness (ITT population)

	Mean ± standard deviation (mm)	Median (range)
Before injection (n=13)	0 ± 0	0 (0-0)
1 h after infusion (n=13)	10.3 ± 2.7	10 (6.5-16.5)
Mean change (n=15)*	8.9 ± 4.4†	9.5 (0-16.5)

ITT: intention to treat; *: change was classed as nil for 2 patients whose data were missing; †: p<0.0001, t-test for paired data.

3.1.2 Study 7MN-501FM (1992)

Aim: to record retrospectively the haemostatic efficacy and tolerance of HAEMOCOMPLETTAN P in patients with afibrinogenaemia, hypofibrinogenaemia or dysfibrinogenaemia.

Method:
Retrospective study: data were collected from patients' records.

Inclusion criteria:

Patients with hypofibrinogenaemia, dysfibrinogenaemia or afibrinogenaemia combined with bleeding tendency.

Non-inclusion criteria:

Asymptomatic dysfibrinogenaemia,
Dysfibrinogenaemia combined with thrombotic events.

Endpoint:
Doctor's assessment of treatment efficacy in stopping bleeding or preventing bleeding during surgery. Efficacy was graded very good, moderate or poor.
The doctor's clinical judgement was supported if necessary by measurement of plasma fibrinogen concentration and other tests (activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT)).

Results:
A total of 12 patients were included.
- median age at time of first recorded treatment was 11.5 years (1 day to 29 years).
- eight (8) patients had afibrinogenaemia, 3 had hypofibrinogenaemia and 1 had dysfibrinogenaemia combined with hypofibrinogenaemia.

Follow-up:
Duration of follow-up was between 1 day and 77 months (median = 26.5 months), corresponding to one or more bleeding episodes, surgical procedures or doses of prophylactic replacement therapy.

Treatment given:
A total of 151 injections/infusions were given, from different batches, i.e.1-87 doses per patient.
Treatment duration for a bleeding episode or surgical procedure was 1-12 days (median: 1 day).
Doses given are shown in *Table 2*

Table 2: doses given

	Dose in g/patient	Dose in mg/kg
Median dose (range) given by injection/infusion: (n injections/infusions)		
o Bleeding or surgical procedures	2.00 (0.2-8) (n=62)	63.5 (31.3-222.2) (n= 53)
o Prophylactic administration	2.00 (2-6) (n=89)*	76.9 (52.6-103.4) (n=8)
Total median dose administered per event (n events)		
o Bleeding or surgical procedures	4 (0.2-16) (n=37)	105.5 (35.1-276) (n= 28)
o Prophylactic administration	Identical to median dose/injection	Identical to median dose/injection

*: these data were obtained from records for 3 patients and for 86 of the 89 values, from the same patient.

Clinical efficacy was assessed during 37 bleeding episodes (including during surgical procedures) and as prophylaxis for 89 infusions (3 patients). Severity of bleeding was not stated.
- efficacy was graded as very good for 36 bleeding episodes and moderate for 1.
- no intercurrent bleeding was reported in the 3 patients who were treated prophylactically.

3.1.3 Survey CE1221_1

Aim:
The aim of this retrospective survey was to collect information about congenital fibrinogen deficiency from doctors with experience of it, i.e. characteristics of bleeding, types of treatments used in general and for different types of events.

Method
A questionnaire was sent to selected doctors and the completed questionnaire was returned by email or by fax.
The data collected concerned patients treated with HAEMOCOMPLETTAN P, other fibrinogen concentrates, cryoprecipitate or with a number of these therapies.
Efficacy was graded by the doctor as excellent, good or poor.

Results:
- Nineteen subjects were treated prophylactically, 12 of them with HAEMOCOMPLETTAN P. Data for patients who had intercurrent bleeding did not include information on the type of prophylactic treatment received (HAEMOCOMPLETTAN P, other fibrinogen concentrate or cryoprecipitate).
- Eighty-one subjects were treated on request, 14 of them with HAEMOCOMPLETTAN P. Results of treatment in these patients are shown in *Table 3*

Table 3: results of treatment with HAEMOCOMPLETTAN P

Type of event	grading	n events	n patients*
Minor bleeding	excellent	4	2
	good	6	2
	poor	1	1
Major bleeding	excellent	26	2
	good	28	4
	poor	2	NS
Potentially life-threatening bleeding	excellent	1	1
	good	1	1
	poor	-	-
Minor surgical procedure	excellent	6	2
	good	4	1
	poor	-	-
Trauma	excellent	11	3
	good	20	6
	poor	1	NS

* the corresponding grade is the median per subject for events of the same type; NS: not stated:

3.2. Adverse effects

3.2.1 Study BI3023 2001 (2008)

Viral tolerance endpoints: serology before injection for HIV1 and 2, hepatitis A, B and C, parvovirus B19; on D10 for parvovirus B19; on D14 for hepatitis A; on D45 for HIV1 and 2, hepatitis A, B and C or on D90 for HIV1 and 2 and hepatitis A and B. There was no seroconversion during the trial.
Two patients experienced adverse events classed as mild which were considered to be unrelated to treatment, i.e. epistaxis, gastro-oesophageal reflux, headache and pain.

3.2.2 Study 7MN-501FM (1992)

One patient with afibrinogenaemia had an anaphylactic reaction with severe hypotension, cyanosis of the lips and extremities, abdominal and back pain following the 56th prophylactic infusion. The patient had no adverse events during subsequent infusions; he received a total of 87 infusions.
One patient with afibrinogenaemia undergoing surgery for internal fixation of a femoral neck fracture had a deep venous thrombosis and multifocal pulmonary embolism 15 days after the procedure. He received five doses of HAEMOCOMPLETTAN P, i.e. on the day of the procedure, the following day, and 2, 8 and 17 days afterwards.

3.2.3 Survey CE1221_1 (2003)

Tolerance data were not collected during this survey. Adverse events were reported for two subjects treated with HAEMOCOMPLETTAN P when recording dose changes during prophylactic therapy:
- one patient had an ischaemic stroke followed by a brain haemorrhage (interval between the two events not known).
- one patient had an arterial thrombosis of the leg.

3.2.4 Study BI 3.023 / 7MN-101FM (1994)

The pharmacokinetics section of this study was not used.
Six patients were included, receiving a single 60 mg/kg dose as an intravenous infusion.
Six adverse events were reported in four patients, three of which were considered to have a possible causal relationship with treatment (dyspnoea with raised temperature of 37.6°C, dizziness).
The others (pain in the infused vein and headache, pallor with nausea and shivering) were considered to be unrelated to treatment.

3.2.5 Study 7D-420XX-RS (1990)

This prospective viral tolerance study included four children aged between 1 day and 14 years with congenital fibrinogen deficiency who had never received a blood derivative or plasma. A total of 64 injections from at least 12 different batches were given during the study. Patients were followed-up for 52-57 weeks from the 1st injection.
Three patients who had not been vaccinated against hepatitis B had no seroconversion during follow-up. Liver function tests for these four patients were monitored and no abnormalities suggestive of non-A non-B hepatitis were found. HIV1 serology tests remained negative.
There were no reports of adverse events.

Amendment to report of study 7D-420XX-RS (1994)
This report contains data concerning two additional patients and extension of follow-up for two of the patients already included.
The six patients included were followed up for a total of 52-450 weeks; their serology test results remained negative for HIV1 and hepatitis B; two patients were tested for HIV2, three for hepatitis C and three for hepatitis A: all their serology tests remained negative.

3.2.6 Observational study BI 3.023 / 7D-501FM (1995)

As this prospective observational study concerned off-label use (acquired hypofibrinogenaemia), only the tolerance data were used.
A total of 94 patients were included in the tolerance analysis and 235 injections/infusions were administered. Two patients had an adverse event considered to have a possible causal relationship with the study treatment, i.e. one case of moderate fever and one case of mild fever. One case of pulmonary embolism occurred during treatment but was not considered to be related to treatment. Twenty patients died during the study; these deaths were not considered to be related to treatment (the patients included had serious concomitant disease or serious disease which was the cause of their hypofibrinogenaemia).

3.2.7 Pharmacovigilance data (PSURS)

Between 01 March 2002 and 30 June 2007, 388 497 g of HAEMOCOMPLETTAN P were sold. During this period 15 adverse events were reported:
- 6 allergic/anaphylactic reactions; 4 were considered to be related to treatment, including two serious reactions.
- 4 cases of viral infection (1 hepatitis B and 3 hepatitis C) which were not considered to be related to treatment.
- 5 serious thromboembolisms, 4 of which were considered be related to treatment.

Between 01 July 2007 and 30 June 2010, 540 617 g of RIASTAP/ HAEMOCOMPLETTAN P were sold. During this period 17 adverse events were reported:
- 1 anaphylactic shock, 1 anaphylactic reaction and 1 case of palpitations, all three serious, were considered to be related to treatment.
- 5 serious thromboembolisms (including 1 death from myocardial infarction) were considered to have a possible causal relationship with treatment.
- 3 cases of hepatitis C and 1 case of hepatitis A in 3 patients and 1 suspected hepatitis B and HIV1 infection in 1 patient, were not considered to have a causal relationship with treatment.
- 2 respiratory adverse events. 1 case of gangrene, 1 severe headache and 1 of pulmonary oedema were not considered to be related to treatment.

3.3. Conclusion

One single-dose study found an increase in maximum clot firmness (MCF) after administration of RIASTAP/ HAEMOCOMPLETTAN P. The SPC states that haemostatic efficacy in acute bleeding episodes, and its correlation with MCF, are being verified in a post-marketing study.
A retrospective efficacy study included 12 patients followed up for between 1 day and 77 months. Efficacy was graded very good in 36 bleeding episodes/37 and average in 1 case. No intercurrent bleeding was reported in the three patients treated prophylactically.
In two prospective studies that included a total of 21 patients, serology tests were performed before administration of RIASTAP/ HAEMOCOMPLETTAN P. For 21 patients tested, no seroconversion was recorded for HIV1 or hepatitis B; for 17 patients tested, no seroconversion was recorded for HIV2; for 18 patients tested, no seroconversion was recorded for hepatitis A and C.
The adverse effects recorded during clinical trials and pharmacovigilance studies were anaphylactic reactions, thromboembolism and elevated temperature.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Congenital hypofibrinogenaemia, dysfibrinogenaemia and afibrinogenaemia are rare diseases characterised by bleeding that may be life-threatening.

The proprietary medicinal product is used as replacement therapy.

The efficacy/adverse effects ratio is high.

> Congenital fibrinogen deficiencies are serious but rare diseases. They are therefore a small burden in terms of public health.
> Improvement in the management of fibrinogen deficiencies could constitute a public health need in the context of an established priority (rare diseases plan). However, this need is currently covered by existing therapies (e.g. CLOTTAFACT).
> In view of the available data (noncomparative studies, in small populations), there is no evidence to suggest that RIASTAP will have any impact in terms of morbidity, mortality or quality of life.
> In terms of organisation of care, the availability of a second fibrinogen-based proprietary medicinal product for patients with a congenital deficiency would be useful in alleviating problems of supply of these proprietary medicinal products.
> Consequently, as for the product CLOTTAFACT, no public health benefit is anticipated for RIASTAP in this indication.

This proprietary medicinal product is a first-line therapy to treat spontaneous or post-traumatic bleeding in patients with congenital fibrinogen deficiency.

An alternative medicinal product exists (CLOTTAFACT).

The actual benefit of this proprietary medicinal product is substantial.

4.2. Improvement in actual benefit (IAB):

RIASTAP shares the major improvement in actual benefit (level I) of CLOTTAFACT in the treatment of patients with congenital fibrinogen deficiency.

4.3. Therapeutic use

4.3.1 Treatment strategy

In patients with congenital fibrinogen deficiency, fibrinogen infusions are the first-line therapy in bleeding episodes[1,2].

An AFSSAPS document [3] concerning the indications for allogeneic fresh frozen plasma (FFP) states as a general rule that transfusion of FFP is only recommended in cases which combine either bleeding, or a procedure carrying a risk of bleeding, with a serious haemostasis deficiency defined as:

- fibrinogen < 1 g.L-1 (particularly if platelet count is < 50.109 L-1),
- PT approx. < 40%
- APTT > 1.5- 1.8 times the control value.

However, treatment of bleeding in patients with congenital hypofibrinogenaemia or afibrinogenaemia is not one of the indications mentioned.
Another AFSSAPS document states that there is no alternative therapy to fibrinogen in patients with congenital afibrinogenaemia, particularly in patients with disorders involving bleeding events[4].

Two other documents[1, 2] mention the use of fresh frozen plasma if fibrinogen is not available.

4.3.2 Place of the proprietary medicinal product in the treatment strategy

RIASTAP is a first-line therapy for bleeding in patients with congenital hypofibrinogenaemia or afibrinogenaemia with bleeding tendency.

4.4. Target population

According to ORPHANET data[5], the prevalence of congenital fibrinogen deficiency is 0.15/100 000, which on the basis of the provisional INSEE population census in 2010, would represent 95 individuals.

4.5. Transparency Committee recommendations

The committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and the dosage in the Marketing Authorisation.

4.5.1 Packaging: Appropriate for prescription conditions

---

1 ORPHANET – déficit congénital en fibrinogène [congenital fibrinogen deficiency] (in French) – www.orpha.net – October 2009
2 Keeling D *et al*. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Centre Doctor's Organisation (UKHCDO) guideline. Approved by the British committee for standards in haematology. Haemophilia 2008; 14: 671-84
3 AFSSAPS - Transfusion de plasma frais congelé : produits, indications – recommandations – August 2002.
4 AFSSAPS - Point de situation sur les approvisionnements en fibrinogène pour le territoire national - Proposition de hiérarchisation des indications du fibrinogène en situation de tension forte sur les approvisionnements pour le marché français. 21 November 2008
5 ORPHANET Reports – Prévalence des maladies rares : données bibliographiques – November 2010. http://www.orpha.net/orphacom/cahiers/docs/FR/Prevalence_des_maladies_rares_par_prevalence_decroissante_ou_cas.pdf