HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
09 July 2014

DEFITELIO 80 mg/ml, concentrate for solution for infusion - 2.5 ml vial

B/10 (CIP: 34009 585 794 6 2)

Applicant: GENTIUM SPA

INN	Defibrotide
ATC Code (2013)	B01AX01 (Other antithrombotic agents)
Reason for the request	**Inclusion**
List concerned	**Hospital use (French Public Health Code L.5123-2)**
Indications concerned	**"DEFITELIO is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy. It is indicated in adults and in adolescents, children and infants over 1 month of age."**

Actual Benefit	**The actual benefit of DEFITELIO is moderate.**
Improvement in Actual Benefit	**In light of the available data which have a low level of evidence while there are study designs only requiring a few patients, due to the severity of the disease and the absence of an alternative, the Committee considers that DEFITELIO provides a minor improvement in actual benefit (IAB IV) in the therapeutic strategy for treatment of severe hepatic VOD post-HSCT.**
Therapeutic Use	**Defibrotide (DEFITELIO) is a first-line treatment for hepatic VOD diagnosed as severe in adults, adolescents, children and infants over 1 month of age.**
Committee recommendations	**The Committee will re-assess DEFITELIO within a maximum period of 3 years based on survival and safety data (nature, frequency and severity of adverse events) obtained from all newly treated patients. These data will be provided by the company.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	18/10/2013 (centralised procedure) <u>Marketing Authorisation granted under exceptional circumstances</u>: Prior to launch, the Marketing Authorisation Holder (MAH) must set up a patient registry to assess the long-term safety, health outcomes and patterns of use of defibrotide during normal use. This must be an observational, multicentre, multinational and prospective disease registry of patients diagnosed with severe hepatic VOD following HSCT and which enrols patients receiving treatment with defibrotide, other treatments or supportive care. The MAH must ensure that the information concerning all safety problems identified in the most recent version of the risk management plan are collected. The MAH must also ensure that all healthcare professionals who may prescribe defibrotide receive information on the importance of the registry and how to enrol patients.
Prescribing and dispensing conditions/special status	List I Orphan medicinal products Medicine for hospital prescription Medicine for hospital prescription restricted to haematologists or doctors trained in blood diseases. Medicine with temporary authorisation for use by a named patient [ATU nominative in French] since 2009

ATC Classification	2013	
	B	Blood and blood forming organs
	B01	Antithrombotic agents
	B01A	Antithrombotic agents
	B01AX	Other antithrombotic agents
	B01AX01	defibrotide

02 BACKGROUND

This is a review of the application for inclusion of the proprietary medicinal product DEFITELIO 80 mg/ml, concentrate for solution for infusion, on the list of medicinal products approved for hospital use.

Defibrotide, active ingredient of DEFITELIO, is a sodium salt of a complex mixture of porcine-derived, single-stranded oligonucleotides intended to treat severe hepatic veno-occlusive disease (VOD) following haematopoietic stem-cell transplantation (HSCT).

DEFITELIO has had temporary authorisation for use by a named patient [ATU nominative in French] in France since 2009; 895 patients have been treated including 380 for the treatment of VOD.

An initial MA request was submitted to the EMA on 03/05/2011 for the following indications:
- Prevention of hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.
- Treatment of hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.

The CHMP [Committee for Medicinal Products for Human Use] refused the MA request for these indications on 21 March 2013.

On 2 April 2013, the company applied for a review of the case by the CHMP. Following this review and the company hearing on 22 July 2013, MA was finally granted to DEFITELIO only for treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome in haematopoietic stem-cell transplantation therapy.

03 THERAPEUTIC INDICATION

"DEFITELIO is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.

It is indicated in adults and in adolescents, children and infants over 1 month of age."

04 POSOLOGY

"DEFITELIO must be prescribed and administered to patients by specialised physicians experienced in the diagnosis and treatment of complications of HSCT.

Dosage
The recommended dose is 6.25 mg/kg body weight every 6 hours (25 mg/kg/day).
There is limited efficacy and safety data on doses above this level and consequently it is not recommended to increase the dose above 25 mg/kg/day.
DEFITELIO should be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve.

Renal and hepatic impairment
No formal pharmacokinetic studies have been performed in patients with renal or hepatic impairment, however, the medicinal product has been used in clinical trials in patients developing renal and hepatic impairment without dose adjustment with no safety issues identified. No dose adjustment is therefore recommended but careful monitoring of patients should be undertaken.

Paediatric population
The recommended dose for children aged 1 month to 18 years is the same mg/kg dose as for adults i.e. 6.25 mg/kg body weight every 6 hours.

Method of administration
DEFITELIO is administered by intravenous infusion, over two hours.

DEFITELIO should always be diluted prior to use. DEFITELIO can be diluted with 5% glucose solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion, to a suitable concentration to permit infusion over 2 hours. The total volume of infusion should be determined based on the individual's patient weight. The final concentration of DEFITELIO should be in the range of 4 mg/mL to 20 mg/mL.
Vials are intended for a single use and unused solution from a single dose must be discarded. "

05 THERAPEUTIC NEED

Hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome is defined as toxic damage of the hepatic sinusoidal endothelial cells, then non-thrombotic obstruction of the hepatic veins through concentric subendothelial thickening due to oedema then incipient fibrosis.[1,2,3] This results in a hypofibrinolytic and procoagulant state in the patient which appears to be the main pathophysiological mechanism of this disease.
The disease is mainly due to toxicity from the conditioning regimen with myelosuppressive chemotherapy in preparation for the haematopoietic stem-cell transplantation, affecting 10 to 60% of transplant patients, depending on the conditioning regimen. The disease can also occur following chemotherapy or radiotherapy.

It is characterised by the onset of cholestatic jaundice, painful hepatomegaly, portal hypertension and fluid retention during the first 3 to 4 weeks following haematopoietic stem-cell transplantation (HSCT) resulting in weight gain, oedema and ascites. Hepatic impairment manifests as coagulopathy and hepatic encephalopathy can occur.

The clinical diagnosis[4] of hepatic VOD is mainly based on the clinical and biological criteria validated and described in the Seattle and Baltimore criteria **(Table 1).**

Table 1: Seattle and Baltimore diagnostic criteria

Modified Seattle criteria[5]	**Baltimore criteria[6]**
Presence of at least two of the following criteria during the 20 days post-HSCT: • Elevated serum bilirubin ≥ 2 mg/dl (≈ 34 µg/l); • Hepatomegaly with right upper quadrant pain; • Ascites and/or unexplained weight gain > 2% compared with baseline weight.	Elevated serum bilirubin ≥ 2 mg/dl (≈ 34 µg/l) before day 21 post-HSCT and at least two of the following criteria: • Hepatomegaly (most often, painful); • Ascites • Weight gain ≥ 5% compared with baseline weight.

The severity of the hepatic VOD is also based on clinical criteria4,[5] **(Table 2)**.

[1] Carreras E. Veno-occlusive disease of the liver after hemopoietic cell transplantation. Eur J Haematol. 2000; 64: 281-91.
[2] Defitelio: EPAR (European public assessment report). 2013.
[3] Orphanet : maladie veino-occlusive hépatique. Available online: [URL] : http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=FR&Expert=890.
[4] Dignan FL, Wynn RF, Hadzic N, Karani J, Quaglia A, Pagliuca A et al. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Br J Haematol. 2013; 163: 444-57
[5] McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med 1993; 118: 255-67
[6] Jones RJ, Lee KS, Beschorner WE, et al. Veno-occlusive disease of the liver following bone marrow transplantation. Transplantation 1987; 44: 778-83

Table 2: Hepatic VOD severity criteria

Mild hepatic VOD	**Clinically evident VOD and spontaneous resolution (no treatment)**
Moderate hepatic VOD	**VOD requiring specific treatment but resolves completely by day +100 post-transplantation**
Severe hepatic VOD	**VOD results in the death of the patient or VOD not resolved by day +100 post-transplantation ± multiple organ dysfunction syndrome**

From the initial signs, progress may be self-limiting or serious with rapid progression towards death.

Severe hepatic VOD is defined by multiple organ dysfunction syndrome (MODS); generally with acute renal failure (patient dialysed or serum creatinine doubled) or respiratory failure (patient requiring ventilation or oxygen therapy with oxygen saturation < 90% in ambient air) or encephalopathy.
Severe cases of the disease have a poor prognosis with elevated mortality (up to 90%). The major factors of poor prognosis are weight gain and elevated serum bilirubin.[3,7]
No curative or prophylactic treatment for hepatic VOD has been approved in the USA or in Europe. The therapeutic need for this complication is not met.
The main prophylactic measure in the context of haematopoietic stem-cell transplantation consists of reducing the intensity of the conditioning regimen.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

There are no clinically relevant comparators to defibrotide with Marketing Authorisation in this indication.

06.2 Other health technologies

No medicinal product has MA in this indication, nevertheless certain medicinal products are used without MA:[4] Recombinant plasminogen activator molecule (ACTILYSE), N-acetylcysteine, methylprednisolone.
Transjugular intrahepatic portosystemic shunt (TIPS) can also be performed in certain cases.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

DEFITELIO is currently not marketed in any country but has had an early access program for the European market since 2009. The medicinal product was made available by the company in 36 countries on a compassionate use basis between December 1998 and March 2009.

[7] Bearman SI, Anderson GL, Mori M, et al. Venoocclusive disease of the liver: development of a model for predicting fatal outcome after marrow transplantation. J Clin Oncol. 1993; 11: 1729-36

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

Evaluation of defibrotide (DEFITELIO) efficacy is mainly based on a phase III, historical cohortstudy in terms of the percentage of complete remission (CR) of severe hepatic VOD (veno-occlusive disease) by day +100 post-HSCT (study 2005-01) The company also provided interim results from a second phase III, non-comparative study (2006-05) evaluating the efficacy and safety of defibrotide in patients with severe hepatic VOD.

8.1.1 Study 2005-01

Table 3: Study description

	Study 2005-01
Principal study objective	To demonstrate the efficacy of defibrotide in patients with severe hepatic VOD in terms of complete response (CR) (defined by total bilirubin < 2 mg/dl and resolution of MODS) by day +100 post-HSCT (haematopoietic stem-cell transplantation).
Method	Phase III study evaluating the efficacy and safety of defibrotide (25 mg/kg/day) in the treatment of severe hepatic VOD in patients who have received a HSCT. The results of this study were compared with efficacy data from a historical cohort of untreated patients.
Study population	Defibrotide treatment group population: patients with severe hepatic VOD Population of the historical cohort: patients not treated with defibrotide, having presented severe hepatic VOD between 1995 and 2007, from a review of medical records performed in each of the investigating centres participating in the study.
Inclusion criteria	• clinical diagnosis of hepatic VOD defined according to the Baltimore diagnostic criteria, by the presence of jaundice (bilirubin concentration ≥ 2 mg/dl) and at least two of the following clinical criteria by day +21 post-HSCT at the latest: ascites, weight gain ≥ 5% compared with the weight measured at inclusion of the patient, hepatomegaly. • Severe VOD associated with MODS by day +28 post-HSCT at the latest such as: - Renal failure (serum creatinine ≥ 3 times the value at inclusion of the patient, creatinine clearance or glomerular filtration rate (GFR) ≤ 40% of the initial value or patient on long-term dialysis); - Respiratory failure (oxygen saturation ≤ 90% in ambient air, or requiring ventilation/oxygen therapy).
Non-inclusion criteria	- History of hepatic cirrhosis, - Other diagnosis explaining the ascites, weight gain and jaundice such as fulminant viral hepatitis, - Documented diagnosis of grade 2-4 graft-versus-host reaction according to the Center for International Bone Marrow Transplant Registry (CIBMTR) severity index involving the liver or intestines, or grade 3 or higher according to the CIBMTR severity index involving the skin. - Previous solid organ transplantation, - Dependency on dialysis during admission of the patient, before and/or at the time of HSCT, or dependency on oxygen therapy during conditioning regimen prior to the HSCT. - Administration of a medicinal product increasing the haemorrhagic risk (heparin or other anticoagulants administered within 12 hours, unless they are administered as part of central venous line maintenance, fibrinolytic instillation for occlusion of the central venous line, intermittent dialysis or ultrafiltration during continuous veno-venous haemofiltration),

	- Acute, clinically significant, uncontrolled haemorrhage, - Haemodynamic instability, defined by the necessity to administer several vasopressors or inability to maintain mean arterial pressure with a single vasopressor. The same non-inclusion criteria were applied for eligibility of patients in the historical group, except: - The "administration of treatment increasing the risk of haemorrhage" non-inclusion criterion was not applied to patients in the historical group as they were often treated with an anti-thrombotic as part of the treatment of the severe hepatic VOD. - An additional non-inclusion criterion was added: "Administration of defibrotide treatment".
Treatment groups	**ITT population:** *For the treatment group*: all patients who consented to participate in the study and meeting the inclusion/non-inclusion criteria. *For the historical group*: all patients considered by the study committee as having severe hepatic VOD and not presenting any non-inclusion criteria.
Course of the study	For the patients included in the treatment group: 1. Inclusion/evaluation visit, 2. Treatment phase in hospital with daily clinical evaluation to evaluate the efficacy and safety of the treatment (minimum of 21 days and until discharge of the patient), 3. End of treatment visit (3 days after discontinuation of defibrotide at the latest), 4. Follow-up visit No. 1 on day +100 post-HSCT, 5. Follow-up visit No. 2 on day +180 post-HSCT,
Primary efficacy endpoint	**Percentage of complete remission (CR) of severe hepatic VOD by day +100 post-HSCT** defined as the presentation of two of the following criteria: - Bilirubin level < 2.0 mg/dl, - Resolution of MODS defined as: • Resolution of renal failure: serum creatinine < 1.5 times that measured at inclusion or equal to the upper limit of normal corresponding to the patient's age and renal clearance and/or GFR > 80% of the value at inclusion by day +100 post-HSCT OR resolution of renal failure maintained until day +100 post-HSCT in patients dependent on dialysis at inclusion or during the study, • Resolution of respiratory failure: oxygen saturation > 90% in ambient air and/or oxygen therapy not required/resolution of dependency on assisted ventilation.
The secondary endpoints included	Secondary efficacy endpoints: - Mortatlity rate by day +100 and day +180. - Time before CR and before the death of the patient (according to the Kaplan-Meier estimation up to day +100 post-HSCT), - Correlation between CR and survival at day +100, - Loss of CR between day +100 and day +180. Secondary safety endpoints: - Frequency and severity of adverse events (AE) and serious AEs (SAE) and their relationship with the study treatment, treatment discontinuation related to an AE, and death. - Vital signs, electrocardiogram, weight, physiological state (according to the Karnofsky score for adults and Lansky for children) - Laboratory examinations.
Calculation of the number of subjects required	A total of 80 patients per group was required to observe a statistically significant difference with a bilateral significance level of 0.01 (statistical power 99%).

Results
This study was conducted in the USA, Canada and Israel (July 2006 - November 2008).
The results were analysed in the ITT population defined as all patients included in the defibrotide group and all patients in the historical cohort group.
The numbers in the ITT population were as follows:
- defibrotide group: n = 102
- historical group: n = 32

The patients had an average age of 26 in the defibrotide group versus 24.9 in the historical group. Male patients accounted for 63% of the defibrotide group and 56% of the historical group. Their mean weight was 53.7 kg (defibrotide) versus 52.8 kg (historical cohort group).

Primary efficacy endpoint
- The percentage of complete remission (CR) of severe hepatic VOD by day +100 post-HSCT was 23.5% (24/102 patients) in the defibrotide treatment group.
- The percentage of complete remission (CR) of severe hepatic VOD by day +100 post-HSCT was 9.4% (3/32 patients) in the historical cohort group.

The adjusted difference between the two groups was 17.3%, CI 99.1% = [-0.9; 35.6], p = 0.0131). This criterion was analysed in the ITT population by the adjustment method using the propensity score.

Among the secondary endpoints:
- The mortality rate at day +100 was 61.8% (63/102 patients) in the defibrotide group.
- The mortality rate at day +180 was 67.6% (69/102 patients) in the defibrotide group.
- The mortality rate at day +100 was 75.0% (24/32 patients) in the historical cohort group.
- The mortality rate at day +180 was 75.0% (24/32 patients) in the historical cohort group.

No difference was observed between the two groups during the comparison test (Fisher's exact test) according to the stratification variables at inclusion (patient ≤ 16 years old, allogeneic transplantation, history of HSCT, patient dependent on ventilation or dialysis at inclusion).

Several statistical and methodological weaknesses should be highlighted:
- the number of patients included in the historical group (32 patients) is far lower than the number of patients originally planned in the statistical analysis design (80 patients). There is an imbalance between the two groups in terms of the number of included patients.
- the patients in the historical cohort were included between 1995 and 2007 which presents a risk of bias regarding the treatment of these patients which has progressed over these twelve years.
- absence of data concerning European patients.
- potential bias linked to a non-randomised, open-label design and to a historical cohort in particular including selection bias, performance bias and measurement bias even though the experimental design appeared justified by the rarity of the disease. Other types of experimental design such as stepped wedge design or possibly adaptive randomisation could have been used.

In conclusion, taking these comments into account, the level of evidence of the results is low. Therefore, these results can only be considered for exploratory purposes and do not enable precise and reliable quantification of the treatment effect.

8.1.2 Study 2006-05

This is an interim analysis of the non-comparative study 2006-05, with the objective of evaluating the efficacy and safety of defibrotide in patients with severe hepatic VOD. It is important to note that a protocol amendment submitted during the study enabled patients with hepatic VOD to be included regardless of the severity.
The primary objective of this study was to provide and treat patients with severe hepatic VOD with defibrotide (use of a treatment undergoing investigation permitted by American law).
The secondary objectives of this study were:

- To obtain additional data on the use, tolerability and safety of use of defibrotide in the context of treatment of severe hepatic VOD post-HSCT.
- To evaluate the efficacy of defibrotide in a population of patients extracted (patients meeting the inclusion criteria of study 2005-01 presented in the previous chapter) from the total population of this study versus the efficacy results of the historical cohort (n = 32).

The primary efficacy endpoint was:
- The percentage of complete remission (CR) of severe hepatic VOD by day +100 post-HSCT or post-initiation of chemotherapy defined as presentation of the two following criteria: bilirubin level < 2.0 mg/dl and resolution of MODS.[8]
This study was conducted in the USA.
The results were analysed in the extracted population, defined as all patients included as part of the protocol of this study, having undergone transplantation, having received at least one dose of defibrotide and meeting the inclusion/non-inclusion criteria of study 2005-01.
The analysed results in this extracted population were compared with the efficacy results of the historical cohort defined in study 2005-01.

The numbers in the extracted population were as follows: n = 68
The patients had a mean age of 20.8 years in the defibrotide group. 62% of the patients were men. Their mean weight was 50.6 kg.

Primary efficacy endpoint
The percentage of complete remission (CR) of severe hepatic VOD by day +100 post-HSCT was 33.8% (23/68 patients) in the extracted population.
As a reminder, the percentage of complete remission was 9.4% (3/32 patients) in the historical cohort group.
The adjusted difference between the two groups was 21.3%, CI 95% = [6.0; 36.6], p = 0.0064). This criterion was analysed using an adjustment technique based on propensity scores.

Several statistical and methodological weaknesses should be highlighted:
- There is an imbalance between the two groups in terms of the number of patients (low number of patients in the historical cohort).
- Regarding the adjustment method which uses the propensity score, this tool theoretically makes it possible to estimate the efficacy of treatments in similar groups at inclusion regarding which factors in particular led to one treatment being prescribed rather than another (after matching or stratification or through propensity score adjustment). Although this approach is in theory essentially acceptable regarding examined and observed confounding factors, it is unacceptable as regardsother factors, which are disregarded in some cases and for the most part unknown. Whereas randomisation enables balanced distribution at inclusion between each arm depending on these unknown factors, the non-random allocation of treatments in no way guarantees that they will be, even after using the propensity score.
- the patients in the historical cohort were included between 1995 and 2007, which presents a risk of bias in the treatment of these patients which has progressed over these twelve years, particularly the use of reduced intensity conditioning regimen which has reduced the incidence of occurrence of this complication.
- absence of data concerning European patients.

In conclusion, given these comments, the indirect nature of comparison and the biases linked to this type of approach, the level of evidence of the results is low. Therefore, these results can only

[8] Resolution of multiple organ dysfunction syndrome defined by:
• Resolution of renal failure (serum creatinine < 1.5 times that measured at inclusion or equal to the upper limit of normal corresponding to the patient's age AND renal clearance and/or GFR > 80% of the value at inclusion by day +100 post-HSCT OR resolution of renal failure maintained until day +100 post-HSCT in patients dependent on dialysis at inclusion or during the study),
• Resolution of respiratory failure (oxygen saturation > 90% in ambient air AND/OR oxygen therapy not required/resolution of dependency on assisted ventilation).

be considered for exploratory purposes and do not enable precise and reliable quantification of the treatment effect.

8.1.3 Real-life data

The American CIBMTR (Center for International Blood and Marrow Transplant Research) manages an independent registry collecting all the data from allogeneic HSC transplantations performed in the USA and 80% of the autologous transplantations.

Between 01/11/2008 and 31/12/2011, 8341 transplant patients were entered into the database and 275 of them developed hepatic VOD post-transplantation. The diagnosis of severe hepatic VOD was made for 101 patients. The therapeutic management was not reported for 5/101 patients, 55/101 patients were not treated with defibrotide and 41/101 were treated with defibrotide.
The company supplied the EMA with the clinical results at the time of the MA request. However, in the absence of patient characteristics at inclusion, these data were difficult to use; consequently the MA was conditional on the provision of additional data concerning the American registry by 31 January 2014 (characteristics of the patients at their inclusion, risk factors linked to the conditioning regimen, type of HSCT etc.).
These data are shown below:

Clinical results

	Patients treated with defibrotide (n = 41)	Patients not treated with defibrotide (n = 55)
Complete remission of severe VOD by day +100 post-HSCT	51% (21/41)	29% (16/55)
Survival at day +100 post HSCT	39% (16/41)	31% (17/55)
Overall survival (last patient contact)	24% (10/41)	7% (4/55)

Characteristics of the patients in each group
No difference was found between the groups for the following characteristics:
- ethnicity,
- type of disease (AML, ALL, NHL, HL etc.),
- post-transplant progress (remission/non-remission),

Differences were found between the groups for the following criteria:
- age (61% were under 16 years of age in the DEFITELIO group versus 80% over 16 years of age in the untreated group),
- gender (46% of patients were men in the DEFITELIO group versus 72% in the untreated group),
- multiple organ dysfunction syndrome (24% of patients had both renal and respiratory failure in the DEFITELIO group versus 10% in the untreated group),
- type of conditioning chemotherapy,
- type of graft-versus-host reaction prophylaxis

This registry provides additional information, in particular about the untreated patients, data provided only to date for the historical cohort. However, no conclusion on efficacy can be drawn, particularly due to the differences between the groups.

08.2 Adverse Effects

8.2.1 Study 2005-01

The safety results were analysed in the ITT population.
The percentage of treatment-related adverse events was 45% (46/102) in the defibrotide group.

The most common treatment-related adverse events were:
- epistaxis: 7.0% (7/102),
- gastrointestinal haemorrhage: 6.0% (6/102),
- bleeding around the cannula: 6.0% (6/102),
- pulmonary haemorrhage: 6.0% (6/102),
- hypotension: 7.0% (7/102).

The percentage of treatment discontinuations for adverse events was 35% (36/102); this discontinuation was permanent for 30% (31/102) of the patients.
The percentage of treatment discontinuations for treatment-related adverse events was 18% (18/102); this discontinuation was permanent for 16% (16/102) of the patients.

Grade 3, 4 or 5 adverse events were reported in 84% of patients (86/102). The most common were: hypotension (27%), multiple organ dysfunction syndrome (16%), respiratory failure (14%) pulmonary haemorrhage (10%).
Grade 3, 4 or 5 treatment-related adverse events were reported in 26% of patients (27/102). The most common were haemorrhages: pulmonary haemorrhages (5.0%), pulmonary alveolar haemorrhages (4.0%), gastrointestinal haemorrhages (3.0%), haemorrhages around the cannula (2.0%), cerebral haemorrhages (2.0%), coagulopathy (2.0%) but also the onset of hypotension (5.0%).

Finally, the percentage of deaths reported during the study was 66% (66/102). Ten deaths following the onset of haemorrhage (10%) were attributed to the treatment.

8.2.2 Amended study 2006-05

To analyse the safety, the study patients were analysed in the total population of this study (n = 183) namely all the patients included in this study and having received at least one dose of defibrotide regardless of the severity of the hepatic VOD. The profile of these patients therefore differs from the MA population; this is a group of patients with milder disease.

The percentage of treatment-related adverse events was 22% (40/183).

The most common treatment-related adverse events were:
- epistaxis: 3.0% (6/183),
- gastrointestinal haemorrhage: 3.0% (6/183),
- haematuria: 3.0% (6/183),
- pulmonary haemorrhage: 6.0% (11/183),
- hypotension: 5.0% (9/183).

The percentage of treatment discontinuations for adverse events was 38% (69/183); this discontinuation was permanent for 32% (59/183) of the patients.
The percentage of treatment discontinuations for treatment-related adverse events was 14% (26/183); this discontinuation was permanent for 11% (20/183) of the patients.

Grade 3, 4 or 5 adverse events were reported in 65% of patients (119/183). The most common were: multiple organ dysfunction syndrome (21%), progression of the hepatic veno-occlusive disease (19%), respiratory failure (11%), renal failure (13%), hypotension (10%).

Grade 3, 4 or 5 treatment-related adverse events were reported in 13% of patients (24/183). The most common were haemorrhages: pulmonary haemorrhages (5.0%), pulmonary alveolar haemorrhages (2.0%), gastrointestinal haemorrhages (3.0%), cerebral haemorrhages (2.0%) but also the onset of hypotension (2.0%).

Finally, the percentage of deaths reported during the study was 47% (86/183). Three deaths following the onset of haemorrhage (2%) were attributed to the treatment.

8.2.3 Pooled data from the four DEFITELIO clinical development studies

The company provided pooled safety data from the four studies performed during the clinical development of this proprietary medicinal product.
In total, 419 patients who received at least one dose of defibrotide at a dose of 25 mg/kg as part of hepatic VOD (regardless of the severity) were extracted from these studies:
- study 2005-01 (n = 102 patients),
- study 2006-05 (n = 183 patients),
- phase II, randomised, open-label study 99-118, the objective of which was to compare the efficacy and safety of defibrotide treatment at a dose of 25 mg/kg/day versus 40 mg/kg/day in patients with severe hepatic VOD (n = 74 patients having received the 25 mg/kg/day dose),
- phase III, randomised, open-label prophylaxis study 2004-000592-33, the objective of which was to evaluate the efficacy of defibrotide 25 mg/kg/day as a post-HSCT prophylaxis versus no prophylaxis, in the prevention of hepatic VOD in children. The study protocol enabled all patients who were randomised and subsequently developed hepatic VOD to receive defibrotide treatment, thus the safety data of patients treated with defibrotide (n = 60 patients having developed hepatic VOD during this study and having been treated with defibrotide) were extracted.

For all these patients:
The percentage of treatment-related adverse events was 25% (106/419).

The most common treatment-related adverse events were:
- gastrointestinal haemorrhage: 4.0% (17/419 patients),
- cerebral haemorrhage: 2.0% (8/419),
- epistaxis: 4.0% (15/419),
- pulmonary alveolar haemorrhages: 2.0% (10/419),
- pulmonary haemorrhage: 4.0% (17/419),
- hypotension: 5.0% (19/419).

The percentage of treatment discontinuations for adverse events was 24% (102/419); this discontinuation was permanent for 22% (91/419) of the patients.
The percentage of treatment discontinuations for treatment-related adverse events was 11% (44/419); this discontinuation was permanent for 9% (37/419) of the patients in this group.

Grade 3-4 adverse events were reported in 59% of patients (247/419). The most common were: hypotension (16%), renal failure (11%), respiratory failure (8%) progression of the hepatic veno-occlusive disease (6%).
Grade 3-4 treatment-related adverse events were reported in 15% of patients (63/419). The main events were haemorrhages: pulmonary haemorrhages (3.0%), pulmonary alveolar haemorrhages (2.0%), gastrointestinal haemorrhages (3.0%), cerebral haemorrhages (1.0%) but also the onset of hypotension (3.0%).
Finally, the percentage of deaths reported during these studies was 43% (180/419). Six deaths following the onset of haemorrhage (1%) were attributed to the treatment.

In conclusion, the declared adverse events are similar between the four studies despite the different population profiles: age, severity of the hepatic VOD, indication for defibrotide.

08.3 Summary & discussion

The evaluation of the efficacy of defibrotide is based on two studies:
- study 2005-01: phase III study which evaluated the efficacy of defibrotide in terms of percentage of complete remission (CR) of severe hepatic VOD (veno-occlusive disease) by day +100 post-HSCT. The results of this study were compared with efficacy data from a historical cohort of untreated patients.
- study 2006-05 (interim results): which evaluated the efficacy of defibrotide in terms of percentage of complete remission (CR) by day +100 post-HSCT in patients with severe hepatic VOD and extracted (patients meeting the study 2005-01 inclusion criteria) from the ITT population of this study. These results were compared with efficacy data from a historical cohort of untreated patients (n = 32).

The primary efficacy endpoint:
- in study 2005-01, the percentage of complete remission (CR) of severe hepatic VOD by day +100 post-HSCT was 23.5% (24/102 patients) in the defibrotide treatment group.
The percentage of complete remission (CR) of severe hepatic VOD by day +100 post-HSCT was 9.4% (3/32 patients) in the historical cohort group.
The adjusted difference between the two groups was 17.3%, CI 99.1% = [-0.9; 35.6], p = 0.0131).
- in study 2006-05, the percentage of complete remission (CR) of severe hepatic VOD by day +100 post-HSCT was 33.8% (23/68 patients) in the extracted population (population meeting the same inclusion/non-inclusion criteria as those defined in study 2005-01).
The adjusted difference between the treated group and the 2005-01 historical cohort was 21.3% (CI 95% = [6.0; 36.6], p = 0.0064).

These studies present several statistical and methodological weaknesses, elaborated in the "efficacy" section of this file, in particular the number of patients included in the historical group (32 patients) which is less than the number of patients originally planned in the statistical analysis design, but also the presence of potential biases (selection bias, performance bias and measurement bias) secondary to a non-randomised and open-label approach even though the experimental design appeared justified by the rarity of the disease. Consequently, the evidence level of the results is low and does not enable precise and reliable quantification of the treatment effect.

The Committee regrets that no study with a good level of evidence has been conducted. Considering the large number of patients included, in particular in the temporary authorisation for use [ATU] and the existing methods, a study could have been conducted with a limited number of patients while maintaining a good level of evidence.

The safety evaluation of defibrotide is mainly based on the pooled data from the four studies of the defibrotide clinical investigation plan (phase III studies 2005-01 and 2006-05, phase III study 99-118, phase III prophylaxis study 2004-000592-33), namely 419 patients who received at least one dose of defibrotide at a dose of 25 mg/kg as part of hepatic VOD (regardless of the severity).
The main treatment-related adverse events were: gastrointestinal haemorrhages (4%), pulmonary haemorrhages (4%), epistaxis (4%) and hypotension (5%). The percentage of treatment discontinuations due to adverse events was 24% (102/419). The percentage of treatment discontinuations for treatment-related adverse events was 11% (44/419). Grade 3-4 adverse events were reported in 59% of patients (247/419). The main events were: hypotension (16%), renal failure (11%), respiratory failure (8%) progression of the hepatic veno-occlusive disease (6%).
Grade 3-4 treatment-related adverse events were reported in 15% of patients (63/419). The main events were haemorrhages: pulmonary haemorrhages (3.0%), pulmonary alveolar haemorrhages (2.0%), gastrointestinal haemorrhages (3.0%), cerebral haemorrhages (1.0%) but also the onset of hypotension (3.0%).
Finally, the percentage of deaths reported during these studies was 43% (180/419). Six deaths following the onset of haemorrhage (1%) were attributed to the treatment.

The safe use profile of defibrotide is marked by a risk of haemorrhage, identified in the RMP.

08.4 Planned studies

The CHMP required the Marketing Authorisation Holder (MAH) to set up a patient registry to assess the long-term safety, health outcomes and patterns of use of defibrotide during normal use. This must be an observational, multicentre, multinational and prospective disease registry of patients diagnosed with severe hepatic VOD following HSCT and which enrols patients receiving treatment with defibrotide, other treatments or supportive care. The MAH must ensure that the information concerning all safety problems identified in the most recent version of the risk management plan are collected. The MAH must also ensure that all healthcare professionals who may prescribe defibrotide receive information on the importance of the registry and how to enrol patients.

For March 2014, the MAH will present the results of the SK-HEP-1 trial performed on cells (and a proposition to include the trial as an additional routine test for quality control for batch release and as a stability test both for the active ingredient, defibrotide, and the finished product).

Finally, DEFITELIO is the subject of a risk management plan set up when its Marketing Authorisation was obtained.
Significant identified and potential risks of the RMP to be provided in the PSUR:
Identified risks
- Haemorrhages (including gastrointestinal and pulmonary haemorrhages and epistaxis, without being limited to these)
- Hypotension
- Coagulopathy
- Immunogenicity (allergic reactions or hypersensitivity)

Potential risks
- Injection site reactions / Infections / Septicaemia
- Thromboembolic events
- Immunogenicity (production of antinuclear antibodies)
- Reproductive toxicity

09 THERAPEUTIC USE

Prevention of VOD is mainly linked to reducing the intensity of the conditioning regimen with myelosuppressive chemotherapy prior to the haematopoietic stem-cell transplantation. In recent years, the incidence of occurrence of hepatic VOD has reduced through management modification: the high-risk patients are identified, reduced intensity conditioning regimen is preferred, chemotherapy protocols without cyclophosphamide have been implemented, treatments based on norethisterone are no longer used, concomitant administration of hepatotoxic medicinal products is avoided, the patients have transplantations earlier, and the general state of health of the patient at the time of transplantation is better.

Current first-line treatment of severe hepatic VOD is therefore limited to symptomatic treatment; no medicinal product has MA in this indication. The international guidelines4,[9] advise using defibrotide as treatment for hepatic VOD. In addition, other proprietary medicinal products are used without MA4 in this indication: recombinant plasminogen activator molecule (ACTILYSE), N-acetylcysteine, methylprednisolone.
Transjugular intrahepatic portosystemic shunt can also be performed in certain cases.

Defibrotide (DEFITELIO) is a first-line treatment for severe hepatic VOD in adults, adolescents, children and infants over 1 month of age.

[9] EBMT/ESID guidelines for haematopoietic stem cell transplantation for primary immunodeficiencies.

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

◗ Severe hepatic veno-occlusive disease is life-threatening in the short-term due to the multiple organ complications that it can cause.

◗ It is intended as curative therapy.

◗ The efficacy/adverse effects ratio is modest, in the absence of precise and reliable quantification of the treatment effect and risk of haemorrhage.

◗ At this stage of the disease, there is no treatment alternative that has been validated.

◗ It is a first-line therapy.

◗ Public health benefit: Even though severe hepatic veno-occlusive disease, also called sinusoidal obstruction syndrome (SOS), is a serious disease occurring in the context of haematopoietic stem-cell transplantation (HSCT), its public health burden is low due to the limited number of patients involved.
Improvement in the management of HSCT is a public health need that is an established public health priority (Transplant Plan 2012-2016, transplant activity in France[10]).
In light of the available clinical data from the two phase III trials versus historical cohort of untreated patients, in particular revealing a percentage of complete remissions of severe hepatic VOD by day +100 post-HSCT which is higher on DEFITELIO but with a low level of evidence, the expected impact of the DEFITELIO proprietary medicinal product in terms of morbidity and mortality cannot be quantified.
It is therefore not possible to determine whether DEFITELIO will be able to provide an additional response to the identified public health need.
In addition, no impact on the organisation of the healthcare system is expected (not documented).
Consequently, in the current state of knowledge, it is not expected that DEFITELIO will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of DEFITELIO is <u>moderate</u> in the Marketing Authorisation indication.

The Committee gives a favourable opinion for inclusion on the list of medicines approved for hospital use in the indication " treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy. " and at the dosages in the Marketing Authorisation.

[10] Ministerial circular on the inter-regional health organisation plans: Hospital and Organisation of Care Directorate (DHOS) circular 14/02/2007 relating to organ transplant and haematopoietic stem-cell transplant activities

010.2 Improvement in actual benefit (IAB)

In light of the available data which have a low level of evidence even though there are study designs only requiring a few patients, and due to the severity of the disease and the absence of an alternative, the Committee considers that DEFITELIO provides a minor improvement in actual benefit (IAB IV) in the therapeutic strategy for treatment of severe hepatic VOD post-HCST.

010.3 Target population

The target population of DEFITELIO is composed of all adult, adolescent, children and infant patients aged over 1 month with severe hepatic VOD following HSCT.

The prevalence of hepatic VOD has been estimated at 13.7% according to the Coppell at al. meta-analysis.[11] This percentage is applied to all allogeneic and autologous HSCTs identified by the French Biomedicine Agency for 2012; in France (4316 patients, 2630 patients of which had an autologous transplant and 1686 patients an allogeneic transplant),[12] the number of patients presenting hepatic VOD could be estimated at around 591 per year.
The prevalence of severe hepatic VOD has been estimated in the literature at between 28%[13] and 48%[14] (hepatic VOD defined according to the Baltimore criteria, criteria chosen for carrying out studies 2005-01 and 2006-05). Therefore, the number of patients with severe hepatic VOD could be estimated between 165 and 283 patients/year.

From these data, the target population for DEFITELIO could be between 165 and 283 patients/year.

For information purposes, DEFITELIO is a proprietary medicinal product available in France with temporary authorisation for use by a named patient [ATU nominative in French]. 380 patients received DEFITELIO in the indication "treatment of diagnosed hepatic VOD" between 2009 and 30 September 2013.

011 COMMITTEE RECOMMENDATIONS

◗ Request for data

The Committee will re-assess DEFITELIO within a maximum period of 3 years based on survival and safety data (nature, frequency and severity of adverse events) obtained from all newly treated patients. These data will be provided by the company.

◗ Packaging

Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.

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[11] Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010; 16: 157-68.
[12] Rapport médical et scientifique du prélèvement et de la greffe en France en 2012, Agence de la Biomédecine.
[13] Carreras E, Bertz H, Arcese W, Vernant JP, Tomás JF, Hagglund H et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. Blood. 1998; 92: 3599-604.
[14] Carreras E, Díaz-Beyá M, Rosiñol L, et al. The incidence of veno-occlusive disease following allogeneic hematopoietic stem cell transplantation has diminished and the outcome improved over the last decade. Biol Blood Marrow Transplant. 2011; 17: 1713-20.