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# Defibrotide in Severe Sinusoidal Obstruction Syndrome: Medicine and Economic Issues

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A B S T R A C T

In Europe, Defitelio (defibrotide) has a Market Authorization in curative treatment of severe sinusoidal obstruction syndrome (SOS) but not in prophylaxis (2013). In France, defibrotide has had a compassionate-use program since 2009. Today, the high cost of defibrotide remains a major hurdle for hospital budgets. Medicine and economic issues were evaluated for the 39 hospitals of the French Public Assistance–Hospitals of Paris (AP-HP). We analyzed literature reviews, consumption, and expenditures through AP-HP data in 2014 and patient profiles with defibrotide in the corresponding diagnostic-related groups (DRGs) and consulted a board of hematologists. Finally, 18 publications were selected. Between 2011 and 2014 consumption increased to €5.2M. In 2014, 80 patients receiving defibrotide were mainly ascribed to the DRG "hematopoietic stem cell transplantation" levels 3 or 4. The tariffs attributed to drugs (€3544 to 4084) cover a small part of treatment costs (€97,524 for an adult). French experts thus recommended a harmonization of indications in prophylaxis (off-label use), improvement of pretransplant care, and optimization of the number of vials used. The economic impact led experts to change their practices. They recommended the restriction of defibrotide use to SOS curative treatment and to high-risk situations in prophylaxis.



## INTRODUCTION

Defibrotide is the unique first-line curative treatment of hepatic veno-occlusive disease, now called sinusoidal obstruction syndrome (SOS) in the more recent nomenclature. SOS is a serious pathology resulting from endothelial damage most commonly seen in the setting of hematopoietic stem cell transplantation (HSCT). SOS is commonly described as a form of toxic liver injury, clinically characterized by the development of hepatomegaly, ascites, and jaundice and histologically by diffuse damage in the centrilobar zone of the liver [1]. Hepatic SOS occurs with a low incidence (between 5% and 40% in adults and pediatric populations receiving a HSCT) [1]. The mortality rate of patients with severe SOS using supportive therapy without defibrotide is estimated to be from 84% [2] to 90% in adults [3] and 62% in children [4].

Defibrotide was granted an orphan drug status for the curative treatment and prophylaxis of SOS by the European Medicines Agency in July 2004 [5] and by the US Food and Drug Administration in May 2003 (for the curative treatment of SOS) and in January 2007 (for SOS prophylaxis). In Europe 1129 patients have received defibrotide through a compassionate-use program since 2009 (French National Authority for Health [HAS]). The goal of the "Temporary Authorization for Use" program granted by the French Medicine and Health Product Safety National Agency aims to facilitate early access to new drugs without any Market Authorization (MA) for patients. In March 2013 the European Commission gave a negative opinion on the use of defibrotide in SOS prophylaxis considering the lack of clinical evidence and the weak methodology of the unique randomized multicenter European study in pediatric populations [6].

Finally, in October 2013 the Committee for Medicinal Products for Human Use gave a positive opinion for MA under exceptional circumstances to Defitelio 80 mg/mL (Gentium SPA, Como, Italy) (defibrotide, concentrate for solution for infusion) only for curative treatment of severe SOS in adults and pediatric populations. This decision was justified by the rarity of the disease and incomplete information on this drug explained by ethical reasons preventing to perform a placebo-controlled study. Moreover, a risk management plan was

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required (multicentric, multinational, and prospective observational disease registry of patients diagnosed with severe hepatic SOS after HSCT).

In France a Temporary Authorization for Use status was granted to defibrotide both in prophylaxis (January 2009) and in curative treatments of hepatic SOS (June 2014). During the Temporary Authorization for Use period 895 patients were treated. including 380 for the curative treatment of SOS diagnosed in France (HAS, 2014). The assessment of Defitelio by the Transparence Committee of the HAS in July 2014 revealed an actual moderate benefit and a minor improvement in actual benefit (IAB IV) in the therapeutic strategy for treatment of severe post-HSCT hepatic SOS, considering the severity of the disease but the low level of evidence and the absence of alternative. In conclusion, the HAS considered Defitelio as the first-line treatment for severe diagnosed hepatic SOS. As an innovative and expensive drug, the pharmaceutical company commercializing defibrotide provided the HAS with a cost-effectiveness assessment and a budget impact study of its drug. In early 2016, after a methodologic assessment of the economic evaluation dossier submitted by the company, the Health Economics and Public Health Committee of the HAS ascribed major reserves to the economic data provided by the firm because of limited clinical data and a global weak methodology of the economic model used for the cost-effectiveness and budget impact analysis [7] . It can be noted that the evaluation only focused on the curative use of defibrotide in SOS and not on its potential off-label use in SOS prophylaxis.

Overall, for high-cost hospital drugs, reserved for hospital use, the French Ministry of Health publishes and updates a list developed at the national level, commonly referred to as the "out-of-DRG list" (diagnostic-related group), which consists of an add-on payment on top of the health funds. This financing system aims first to avoid heterogeneity in costs per DRG and second to avoid an uncontrolled increase of prices because of a lack of interest in negotiation from hospitals, as supplementary funding could reduce hospital price sensitivity [8]. Even if defibrotide is an expensive drug, reserved for hospital use, the French Health Ministry refused to put Defitelio on the "out-of-DRG list," mainly because of the lack of evidence of its efficacy and safety and the undefined target population for this drug. Thus, for now, defibrotide is not eligible for this add-on payment in France, and the high cost of defibrotide remains a major problem for hospital budgets.

Despite its elevated cost, some experts in hematology of the Public Assistance–Hospitals of Paris (AP-HP; 39 public Parisian hospitals, which is the largest public hospital group in Europe) continue to use defibrotide in curative and prophylactic treatments (off-label use) for different clinical cases. The framework of these practices in Parisian hospitals takes place in a 2-sided context, a public health problem and economic constraints. Therefore, the aims of this work were to assess the scientific interest of defibrotide (curative and prophylactic treatment of SOS) by analyzing its actual benefit, to estimate the budget impact of defibrotide use, and to frame its indications in prophylaxis to reduce costs for the 39 AP-HP hospitals.

## METHODS

The AP-HP is the largest public hospital group in Europe, with 22,000 beds; it cares for 12 million patients annually. The Committee on Medicinal Products (COMED) of the AP-HP, in charge of listing the medicines on the hospital drug formulary, recently met the challenge of assessing Defitelio from a medical and economic point of view. To reach a conclusion on this drug, the COMED followed a rigorous decision-making process made up of 4 steps in 2015: scientific assessment, AP-HP economic and demographic data, AP-HP consumption and expenditures data, and expert opinion. This approach complements HAS's opinion, which emitted national recommendations, whereas the COMED gives recommendations for patients hospitalized in the AP-HP.

### *Assessment of Therapeutic Need in Prophylaxis and SOS Curative Treatment*

Benefice-to-risk balance and therapeutic interest of defibrotide were assessed, taking into account evidence-based medicine standards and the latest recommendations regarding SOS treatments. The first part of this work needs to describe efficacy and safety outcomes from the published literature about defibrotide. A literature review was conducted using a PubMed, EMBASE, and Google Scholar search. The terms and key words "defibrotide AND hepatic veno-occlusive disease AND haematopoietic stem cell transplantation" were used. Because existing clinical data are very little (low prevalence of the disease, inclusion difficulties in the studies), we chose wide inclusion criteria.

The inclusion criteria considered for our work were adult and pediatric populations, indications in curative and prophylaxis SOS treatment, the route of administration (i.v.), studies published since 2006, and publications written in English or French. Guidelines, reviews, and prospective and retrospective studies were selected. Titles and abstracts of identified studies were evaluated to determine if they met the eligibility criteria.

Pharmaceutical companies submitted a dossier containing scientific regulatory data, and pharmacists performed a review of literature to determine the role of defibrotide in prophylaxis and curative SOS treatment. Finally, a review of the latest national and international guidelines published by learned societies for the management of SOS was conducted.

### *AP-HP Economic and Demographic Data*

The cost of a cure with defibrotide was calculated for the treatment of an adult and a child according to the posology described in the MA of Defitelio. The cost for a prophylactic treatment by defibrotide was estimated from the posology described in learned societies guidelines.

To determine therapeutic indications of patients treated by defibrotide and their DRGs, an extraction of the French medical information system program for 2014 was performed (medical information available from the Medicalization Program of the Information Systems the AP-HP database). Extracted data provided information about the number of patients receiving defibrotide, their age, the duration of hospitalization, and the main diagnosis associated with the corresponding DRGs this same year for AP-HP hospitals.

The tariffs of the corresponding DRGs in 2015 in function of the severity disease level were consulted in the Official French Guidelines (Official Journal, 11/03/2015; https://www.legifrance.gouv.fr/). The part attributed to drugs into the global DRG rate was determined by an extrapolation of a rate reference, which was provided by a hospital panel and published in 2012 (National Cost Survey, 2012; http://www.scansante.fr). The number of AP-HP patients classified into the DRG in function of the severity level was extracted by the Agency for Information on Hospital Care (www.scansante.fr).

### *AP-HP Consumption and Expenditure Data*

Defibrotide consumption and expenditures in all public hospitals of Paris (AP-HP) were analyzed over the 2011 to 2014 period for the board of experts, and the 2015 data was extracted a posteriori.

### *Scientific Discussion and Expert Opinion*

In June 2015 the COMED consulted AP-HP physicians specializing in hematology working in adult and pediatric hospitals and hospital pharmacists to frame the use of Defitelio within AP-HP hospitals. Experts in hematology of AP-HP hospitals were solicited for opinions.

A declaration of interest with the pharmaceutical industry was required before expertise. Only experts without major links were selected to participate in the expert board. Major links of interest were defined as a principal investigator of a study with defibrotide or a competing product, regular monetary remuneration by a firm commercializing defibrotide or a competing product, or family links between experts of these pharmaceutical companies.

## RESULTS

### *Literature Review*

Thirty potentially relevant studies were identified; 27 studies published after 2006 were eligible. Eighteen publications met the inclusion criteria, 1 of which was a prospective, multicenter, randomized controlled trial (RCT) [6] (Figure 1 and Table 1).