

<Date [DD/MM/YYYY]>

Defitelio (defibrotide): Do not use for prophylaxis of veno-occlusive disease (VOD) after post-hematopoietic stem-cell transplantation (HSCT)

Dear Healthcare Professional,

<Name of Marketing authorization holder >, in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

Summary

- **Study 15-007 comparing defibrotide plus best supportive care (BSC) with BSC as prophylaxis of VOD after HSCT was stopped due to futility**
- **No effect on the primary efficacy endpoint of VOD-free survival by day +30 post-HSCT was seen**
- **Defitelio is not to be used as prophylaxis for VOD**

Background

Defibrotide is an oligonucleotide mixture with demonstrated antithrombotic, fibrinolytic, anti-adhesive and anti-inflammatory actions. Under the commercial name of Defitelio, it was approved under exceptional circumstances in 2013 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.

A prophylaxis study (Study 15-007) using a dosage of 25mg/kg/day by intravenous infusion was conducted in paediatrics (n=198) and adults (n=174) post-HSCT. The most common underlying diseases of patients were acute lymphoblastic leukemia (n=100) 26.9%, acute myelogenous leukemia (n=96) 25.8%, or neuroblastoma (n=57) 15.3%. Patients were randomised to defibrotide plus best supportive care (BSC) or BSC alone.

The study was stopped due to futility. The primary endpoint of VOD-free survival by day +30 post-HSCT was not met; there was no difference when defibrotide plus BSC was compared with BSC alone. The Kaplan-Meier estimates (95% CIs) of VOD-free survival by Day +30 post-HSCT were 66.8% (57.8%, 74.4%) in defibrotide plus BSC and 72.5% (62.3%, 80.4%) in BSC alone. The p-value from the stratified log rank test that compared VOD-free survival over time between the two treatment arms was 0.8504.

By Day +30 post-HSCT, there were 10/190 or 5.7% deaths in defibrotide plus BSC compared to 5/182 or 2.9% deaths in BSC alone. Similar proportions of participants receiving defibrotide plus BSC and those receiving BSC alone experienced TEAEs (99.4% vs 100%, respectively) and serious TEAEs (40.9% vs 35.1%, respectively).

The already well established safety profile of defibrotide during treatment of VOD is mainly characterized by haemorrhage (including but not limited to gastrointestinal haemorrhage, pulmonary haemorrhage, and epistaxis) and hypotension. Defibrotide increases the risk of bleeding and should be withheld or stopped if significant bleeding occurs.

In view of these results and taking the safety profile into account, Defitelio is not recommended to be used as prophylaxis of VOD.

Call for reporting

Healthcare professionals are asked to report any suspected adverse reactions associated with the use of Defitelio in accordance with the national spontaneous reporting system *<include details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>*.

To improve traceability of this biological medicine, the name and the batch number should be clearly recorded in the patient file and be included in any reported suspected adverse event.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone number(s), and a postal address> TO BE COMPLETED LOCALLY

Yours sincerely,

Dr Nora Drove,
VP Medical Affairs, Europe and International, Jazz
Pharmaceuticals, Inc.

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN		
Medicinal product(s)/active substance(s)	Defitelio (defibrotide)	
Marketing authorisation holder(s)	<i>Gentium S.r.l.</i>	
Safety concern and purpose of the communication	Defitelio (defibrotide) not to be used for prophylactic treatment of veno-occlusive disease (VOD) after post-hematopoietic stem-cell transplantation (HSCT)	
DHPC recipients	Haematology/Internal Medicine/Oncology/Paediatric Haematology/ Paediatric Oncology specialists in Bone marrow transplantation (BMT) centres and hospital pharmacists from the ordering centres The target group should be further defined at national level, in agreement with the respective national competent authority.	
Member States where the DHPC will be distributed	All EU/EEA Member States where Defitelio is marketed.	
Timetable		Date
DHPC and communication plan (in English) agreed by PRAC		May 05 2022
DHPC and communication plan (in English) agreed by CHMP		May 19 2022
Submission of translated DHPCs to the national competent authorities for review		May 27 2022
Agreement of translations by national competent authorities		June 03 2022
Dissemination of DHPC		June 13 2022