

13/06/2022

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

Dear Healthcare Professional,

Gentium S.r.l, in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency 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**
- **Use Defitelio only for treatment of severe VOD in HSCT therapy**

### **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 25 mg/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 safety profile of defibrotide during treatment of VOD already well established. The potential side effects are 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 for prophylaxis of VOD.

### ***Call for reporting***

Defitelio ▼ is a black triangle medicine and all suspected adverse drug reactions should be reported to the Yellow Card scheme electronically.

Report via the website <https://yellowcard.mhra.gov.uk>, the free Yellow Card app available from the Apple App Store or Google Play Store, and some clinical IT systems (EMIS, SystemOne, Vision, MiDatabank) for healthcare professionals. Suspected side effects can also be reported by calling 0800 731 6789 for free.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

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***

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Yours sincerely,



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