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IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

13 June 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 Health Products Regulatory Authority (HPRA) 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 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 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

HPRA Pharmacovigilance
Website: www.hpra.ie

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

Jazz Pharmaceuticals Ireland Limited
Tel: +353 1 968 1631
(local phone number within Republic of Ireland)
(outside Republic of Ireland may include an international phone call charge)
Email: medinfo-int@jazzpharma.com

ProPharma Group (Medical Information Vendor/Call Center for Jazz Pharmaceuticals, Inc.)
Olliver Road
Richmond
North Yorkshire
DL10 5HX
United Kingdom

Yours sincerely,

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