Jazz Pharmaceuticals

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Direct Healthcare Professional Communication

09/June/2022

DEFITELIO UPDATE

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

Dear Healthcare Professional,

Biologix, in collaboration with Jazz Pharmaceuticals Ireland Limited, and in agreement with the Saudi Food and Drug Authority (SFDA), would like to inform you of the following important new safety information on Defitelio:

- 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
- Use Defitelio only for treatment of severe VOD in HSCT therapy

Further Information and Recommendations

Defibrotide is an oligonucleotide mixture with demonstrated antithrombotic, fibrinolytic, anti-adhesive and anti-inflammatory actions. Under the commercial name of Defitelio, it was approved for the treatment of severe hepatic veno occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in hematopoietic 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 pediatrics (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 randomized 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 treatment-emergent adverse events (TEAEs) (99.4% vs 100%, respectively) and serious TEAEs (40.9% vs 35.1%, respectively).

The safety profile of defibrotide during treatment of VOD is already well established. The potential side effects are mainly characterized by hemorrhage (including but not limited to gastrointestinal hemorrhage, pulmonary hemorrhage, 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 of Adverse Events

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

The National Pharmacovigilance Centre (NPC):

SFDA Call Center: 19999

E-mail: npc.drug@sfda.gov.sa

Website: https://ade.sfda.gov.sa

Contact information:

Pharmacovigilance department at Biologix:

- Name: Arwa Alenzi
- Email: Pharmacovigilance-ksa@biologixpharma.com
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You may also contact our medical information department at Medinfo@blgx.net if you have any questions about the information contained in this letter or questions on the safe and effective use of Defitelio.

This letter is not intended as a complete description of the benefits and risks related to the use of Defitelio.

For extra copies please contact:
You may also contact our medical information department at Medinfo@blgx.net for extra copies.

Yours sincerely,

Dr Nora Drove

VP Medical Affairs, Europe and International,

Jazz Pharmaceuticals, Inc.

Arwa Alenzi

Qualified Person Responsible for Pharmacovigilance

Biologix

Reference:

1. Grupp S, Corbacioglu S, Kang HJ. et al. A phase 3, randomized, adaptive study of defibrotide versus best supportive care (BSC) for the prevention of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) in patients undergoing hematopoietic cell transplantation (HCT): Preliminary results. ASH Abstract/oral presentation Dec 2021.