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Delivering Innovative Healthcare

אוגוסט 2019

הנדון: עדכון עלון לרופא עבור התכשיר Defitelio®

ההתוויה המאושרת:

Defitelio® is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive 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.

החומר הפעיל: defibrotide 200 mg/ 2.5 ml

רופא/ה, רוקח/ת נכבדים,

חברת מדיסון פארמה מבקשת ליידע על עדכון העלון לרופא לתכשיר *Defitelio*®
העדכון מתייחס למנגנון הפעולה ע"פ נתונים שהצטברו, בסעיף 5.1. להלן השינויים המהותיים:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antithrombotic agents; ATC code: B01AX01.

Mechanism of action

~~In vitro, defibrotide~~ Defibrotide is an oligonucleotide mixture with demonstrated antithrombotic, fibrinolytic, anti-adhesive and anti-inflammatory actions. The mechanism of action is multifactorial. It primarily acts through reducing excessive endothelial cell (EC) activation (endothelial dysfunction), modulating endothelial homeostasis as well as restoring thrombo-fibrinolytic balance. However, the exact mechanism of action of defibrotide is not fully elucidated.

Defibrotide has ~~been shown~~ demonstrated antithrombotic and fibrinolytic effects *in vitro* and *in vivo* by: increasing systemic tissue factor pathway inhibitor (TFPI), tissue plasminogen activator (t-PA) and thrombomodulin (TM) expression; decreasing von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) expression; and enhancing the enzymatic activity of plasmin to ~~bind~~hydrolyse fibrin clots.

In vitro and *in vivo* studies have demonstrated that ~~D~~defibrotide inhibits leukocyte and platelet adhesion to ~~various sites on vascular~~ endothelium by: suppressing P-selectin and vascular cell adhesion molecule-1 (VCAM)-1; interfering with lymphocyte function-associated antigen 1-intercell adhesion molecule (LFA-1-ICAM) mediated leukocyte transmigration; and increasing nitric oxide (NO), Prostaglandin I2 (PGI2) and Prostaglandin E2 (PGE2).

In vitro ~~D~~defibrotide demonstrates anti-inflammatory effects that ~~are involved in cell regulation, providing a stimulus that~~ attenuates the release and production of reactive oxygen species and inflammatory mediators such as interleukin 6, thromboxane A2, leukotriene B4 and tumour necrosis factor-α (TNF-α).

Defibrotide protects ECs from damage and promotes ~~protection of activated endothelial cells. Defibrotide has also been shown to protect endothelial cells from~~ tissue homeostasis by decreasing fludarabine-mediated apoptosis~~,~~ of EC while ~~not impacting~~maintaining its anti-leukemic effect~~. Defibrotide also inhibits~~ and by inhibiting the expression of heparanase, shown in *in vitro* and *in vivo* studies respectively~~contributing to~~

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~~extracellular matrix integrity and thereby tissue homeostasis. It is postulated that these actions protect endothelial cells~~.

~~Also, *in vitro*, defibrotide has been shown to increase tissue-type plasminogen activator (t-PA) function and decrease plasminogen activator inhibitor-1 (PAI-1) activity resulting in a decrease in procoagulant activity and an increase in the fibrinolytic potential of endothelial cells. Defibrotide also has been shown to have a weak profibrinolytic activity *in vitro*.~~

~~The pathophysiology of VOD is multifactorial and complex. Both endothelial cell damage and prothrombotic-hypofibrinolytic state are critical factors in the pathophysiology of this disease.~~

~~Whilst the mechanism of action of defibrotide has not been fully elucidated, *in vitro* data support a role for defibrotide in both endothelial cell protection and the restoration of the thrombo-fibrinolytic balance. However no pharmacodynamics effects from defibrotide have been identified *in vivo*.~~

העלון לרופא נמצא בקישור וכן נשלח לפרסום במאגר התרופות באתר משרד הבריאות וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

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