KAMADA
High Quality Pharmaceuticals

מרץ 2023

**רופא/ה נכבד/ה, רוקח/ת נכבד/ה,**

**חברת קמהדע מבקשת להודיע על עדכון עלון כמפורט להלן, עבור התכשירים:**

**Replenine -VF 500 ; Replenine-VF 1000**

**צורת מינון, צורת מתן : Powder for solution for injection, IV**

**מרכיבים פעילים בהתאם לרישיון:**

Replenine-VF 1000: Factor IX 1000 IU/vial
Replenine-VF 500: Factor IX 500 IU/vial

**<u>התוויה מאושרת:</u>**

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

**<u>מהות השינוי:</u>**
עדכון בפרק משטר המינון, פרק הפרמקודינמיקה, עדכון בחיי מדף לאחר שחזור ובפרק הוראות ההכנה של התכשיר.

**<u>עיקרי העדכונים בעלון :</u>**
החמרות מסומנות בצהוב, שינויים נוספים מסומנים באדום
הזזות מקום של טקסט בין סעיפים בעלון מסומנות באפור
מחיקות מסומנות עם ~~קו חוצה~~

**4.2 Posology and method of administration**

Treatment should be ~~initiated~~ under the supervision of a physician experienced in the treatment of haemophilia.

*Treatment monitoring*

… <u>Dose based on body weight may require adjustment in underweight or overweight patients.</u>

…

<u>When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. This is of importance particularly when changing the laboratory and/or reagents used in the assay.</u>

<u>Posology</u>

... ~~Factor IX products rarely require to be administered more than once daily.~~



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| Degree of haemorrhage/ Type of surgical procedure | Factor IX level required (%) or (IU/dl) | Frequency of doses (hours)/ Duration of Therapy (days) |
|---|---|---|
| … | | |
| More extensive haemarthrosis, muscle bleed or haematoma. | 30-60 | Repeat infusion every 24 hours for 3 to 4 days or more until pain and acute disability are resolved. |
| … | | |

…

Paediatric population

*Children under 12 years of age*

There are limited data on the use of Replenine-VF in children under 12 years of age (see section 5.1).

The recommended dose and dosing frequency in adolescents (aged 12-17 years) are as recommended for adults.

~~In a clinical study in children under six years of age, the median dose of Replenine-VF for prophylaxis was 29.3 IU/kg (95% confidence interval: 25.3 - 33.2 IU/kg) given up to twice weekly; the mean dose to treat a bleed was 26.8 IU/kg (95% confidence interval 15.7 - 37.9 IU/kg).~~

~~Patients should be monitored for the development of factor IX inhibitors. If the expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor IX inhibitor is present. In patients with high levels of inhibitor, factor IX therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.~~

~~See also 4.4.~~

Method of administration

Replenine-VF should be administered via the intravenous route at a rate not exceeding 3 ml per minute. ~~The dose, especially the first dose, should be given slowly (not more than 3 ml per minute).~~



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~~For continuous infusion during and after major surgery, the product should be given intravenously and undiluted by a syringe driver or syringe pump (see 4.2).~~

**5.1 Pharmacodynamic properties**

…In a multicentre, non-randomised, open-label clinical study, 22 patients aged 17-76 years with severe haemophilia B (≤2% activity) were treated either prophylactically (n=6) or on demand (n=16) for a median duration of 44 weeks. Patients on the prophylactic regimen (mean dose of 163 IU/kg per month per patient) experienced 11 bleeds on average during the study and the mean dose used to treat them was 49 IU/kg. Patients treated on demand experienced a mean of 13.4 bleeds during the study and the mean dose used to treat them was 30.4 IU/kg.

Paediatric population

~~From clinical trial experience, young children using prophylactic Replenine-VF experienced less bleeds than those only using it on demand. For doses in children see 4.2.~~

In a multicentre, non-randomised, open-label clinical study in 15 children under 6 years of age (range 0.2-5.6 years) with severe haemophilia B (≤2% activity) for a median duration of 28 weeks. The mean number of bleeds per subject per month was 0.2 bleeds for patients in the prophylaxis group (n=10) and 1.2 bleeds in the on-demand group (n=6).

The mean dose of Replenine-VF for prophylaxis was 29 IU/kg (range: 20-37 IU/kg) given up to twice weekly; the mean monthly dose was 194 IU/kg. The mean dose to treat a bleed was 27 IU/kg (range: 13-53 IU/kg).

**6.3 Shelf life**

~~…When opened, store at 2°C to 25°C and use within one hour.~~

After reconstitution, chemical and physical in-use stability has been demonstrated for 1 hour up to 25°C.

From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the reconstituted medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 1 hour up to 25°C.

**6.6 Special precautions for disposal and other handling**

… Use the product immediately after reconstitution or within 1 hour.



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## Instructions for reconstitution:

### (A) Reconstituting in Full Volume (הוספת תמונות לשלבי ההכנה)

| | |
|---|---|
|  | **Step 1**<br>• Remove the cap from the product vial and clean the top of the stopper with an alcohol swab.<br>• Repeat this step with the water vial.<br>• Peel back the top of the Mix2Vial™ transfer device package but leave the device in the package. |
|  | **Step 2**<br>• Place the blue end of the Mix2Vial™ transfer device on the water vial and push straight down until the spike penetrates the rubber stopper and snaps into place.<br>• Remove the plastic outer packaging from the Mix2Vial™ transfer device and discard it, taking care not to touch the exposed end of the device. |
|  | **Step 3**<br>• Turn the water vial upside down with the device still attached.<br>• Place the clear end of the Mix2Vial™ transfer device on the product vial and push straight down until the spike penetrates the rubber stopper and snaps into place. |
|  | **Step 4**<br>• The water will be pulled into the product vial by the vacuum contained within it.<br>• Gently swirl the vial to make sure the product is thoroughly mixed. Do not shake the vial.<br>• A clear or slightly pearl-like solution should be obtained, usually in about 2 to 2 ½ minutes (5 minutes maximum). |
|  | **Step 5**<br>• Separate the empty water vial and blue part from the clear part by unscrewing anti-clockwise.<br>• Draw air into the syringe by pulling the plunger to the required volume of water added.<br>• Connect the syringe to the white filter.<br>• Push the air in the syringe into the vial. |



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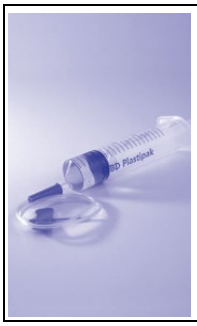
| | |
|---|---|
|  | **Step 6**<br>• Immediately invert the vial of solution which will be drawn into the syringe.<br>• Disconnect the filled syringe from the Mix2Vial™ transfer device.<br>• The product is now ready for administration. Follow the normal safety practices for administration. Use the product immediately after reconstitution, the product must not be stored. |

…

**B) Reconstituting with Half Volume**

…Note: If you have more than one vial to make up your dose, repeat the above steps withdrawing the solution in the vial into the same syringe.

The Mix2Vial™ transfer device supplied with the product is sterile and cannot be used more than once.

עלון התכשיר מתעדכן בהתאם וייושם באריזות התכשיר החל מהאצווה הרלוונטית.

עלוני התכשיר המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים ע"י פניה לבעל הרישום, חברת קמהדע בע"מ (טל' 08-9406472). להלן הקישור למאגר התרופות:

https://israeldrugs.health.gov.il/#!/byDrug



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