הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

תאריך _____12-1-2014_____

שם תכשיר באנגלית ומספר הרישום _121-05-30093_Haemoctin SDH 250 IU_____

121-06-30094_Haemoctin SDH 500 IU

121-07-30095_Haemoctin SDH 1000 IU

שם בעל הרישום _____ Kamada Ltd_____

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

טקסט חדש	טקסט נוכחי	פרק בעלון
Haemoctin® SDH 250, Haemoctin® SDH 500, Haemoctin® SDH 1000	Haemoctin® SDH 250	**Trade name of the medicinal product**
One vial contains 250, 500 or 1000 IU human plasma derived coagulation factor VIII. Haemoctin®SDH 250 or Haemoctin® SDH 500 contains approximately 50 IU/ml human coagulation factor VIII when reconstituted with 5 or 10 ml of water for injections. Haemoctin® SDH 1000 contains approximately 100 IU/ml human coagulation factor VIII when reconstituted with 10 ml of water for injections. The specific activity of Haemoctin® SDH 250, 500 or 1000 is approximately 100 IU/mg protein.	One vial of Haemoctin® SDH 250 contains: *Active substance:*Human plasma derived coagulation factor VIII 250 IU per vial After reconstituting the powder in 5 ml of water for injections, each ml of product contains about 50 IU of human coagulation factor VIII. The specific activity of Haemoctin® SDH 250 is approximately 100 IU/mg protein.	**Qualitative and quantitative composition**
Posology The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. In patients with high levels of inhibitor factor VIII therapy may not be effective, and other therapeutic options should be considered. **Method of administration** Dissolve the preparation as described at 6.6. The product should be administered via the intravenous route. It is recommended not to administer more than 2 - 3 ml Haemoctin® SDH 250, 500 or 1000/min.	The physician must take account of how effective Haemoctin® SDH 250 is for the patient personally when deciding how much and how often it should be administered. ~~Haemoctin® SDH 250 must rarely be administered more than once per day.~~ ~~If the inhibitor is present at levels less than 10 BU per ml, administration of additional human coagulation factor VIII may stop the bleeding. In patients with inhibitor titres above 10 BU or with a strong secondary reaction, the use of (activated) prothrombin complex concentrate (aPCC) or activated factor VII (F VIIa) has to be considered.~~	**Posology and method of administration**
The product contains traces of human proteins other than factor VIII .Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients treated with human coagulation factor VIII should be carefully monitored for the development of	~~The patient should be checked regularly using a biological test (the Bethesda test) for the formation of inhibitors.~~ It is strongly recommended that	**Special warnings and special precautions for use**

<table>
<tr>
<td>inhibitors by appropriate clinical observations and laboratory test. See also 4.8. Undesirable effects.
It is strongly recommended that every time that Haemoctin® SDH 250, 500 or 1000 is administered to a patient, the name and batch number of the product are recorded.

This medicinal product contains a maximum of 3.3 mmol sodium per standard dose of 2000 IU. To be taken into consideration by patients on a controlled sodium diet.</td>
<td>every time a dose of Haemoctin® SDH 250 is given the name and batch number of the product are recorded.</td>
<td></td>
</tr>
<tr>
<td>From introduction in the market until January 2006 a total of about 500 000 standard dosages of Haemoctin® SDH 250, 500 and 1000 were applied. In total 12 cases of suspected development of inhibitors were received from clinical trials, spontaneous reporting and non interventional studies. This corresponds to a reporting frequency of 1 case on 40 864 applications.
➢ 6 of these cases concern transient inhibitors.
➢ In 9 cases the titres of inhibitors were below 10 BU and in 3 cases higher than 10 BU.
➢ 5 cases concern inhibitor development in previously treated patients (PTPs), 3 cases concern inhibitor development in previously untreated patients (PUPs), 1 case concerned a minimally pretreated patient (16 ED) and in 3 cases exposure days were not reported.
➢ 4 cases concern children under 6 years of age, in three of these cases the inhibitors were transient.
For the evaluation of undesirable effects the following frequencies were used: Very common: ≥1/10, Common: ≥1/100 to <1/10, Uncommon: ≥1/1,000 to <1/100, Rare: ≥1/10,000 to <1/1,000, Very rare: <1/10,000, including isolated reports

From clinical trials, non interventional studies, spontaneous reporting and regular literature screening the following adverse reactions were reported on Haemoctin® SDH 250, 500 and 1000:
<table><tr><th>MedDRA Standard System Organ Class</th><th><u>Adverse reactions</u></th><th><u>Frequency</u></th></tr><tr><td>Nervous system disorder</td><td>Haemorrhage brain</td><td>very rare</td></tr><tr><td>Blood and lymphatic system disorders</td><td>Anaemia</td><td>very rare</td></tr><tr><td>Skin and subcutaneous tissue disorder</td><td>Exanthema, urticaria, erythema</td><td>very rare</td></tr><tr><td>Investigations</td><td>Anti factor VIII antibody positive</td><td>very rare</td></tr></table>No cases of transmission of infective agents have been confirmed so far.</td>
<td>~~In the multicenter study of the „Gesellschaft für Thrombose- und Hämostaseforschung" (GTH) with previously untreated patients (PUPs) none of the 6 patients treated with Haemoctin® SDH 250, 500 or 1000 developed an inhibitor. The median number of exposure days in these patients were 47 days (range 2 to 95 days). In 3 children less than 6 years of age (PTPs) and treated with Haemoctin® SDH 250, 500 or 1000 no inhibitor development was observed. In a post marketing surveillance study with previously treated patients (PTPs) performed from 1993 to 2000 none of the 71 patients treated with Haemoctin® SDH 250, 500 or 1000 developed an inhibitor. During this time more than 29.5 Mio. IU Haemoctin® SDH 250, 500 or 1000 have been applied in more than 22000 individual treatments. The following adverse reactions were reported spontaneously to be possibly or probably related to Haemoctin® SDH 250, 500 or 1000 administration with an incidence of less than 0.1 % each: **General:** Abdominal cramps, tightness of the chest, chills, fatigue, fever. **Immune system:** Allergic reactions, anaphylactic shock, development of antibodies to factor VIII neutralising.~~</td>
<td>Undesirable effects</td>
</tr>
<tr>
<td>No case of overdose has been reported.</td>
<td></td>
<td>Overdose</td>
</tr>
<tr>
<td>When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in patient´s circulation.
In patients with high levels of inhibitor factor VIII therapy may not be effective, and other therapeutic options should be considered. Following such treatment options Haemoctin SDH</td>
<td></td>
<td>Pharmacodynamic properties</td>
</tr>
</table>

has been shown to be effective in 11 patients with inhibitors undergoing immune tolerance therapy.		
Plasma factor VIII activity decreases by a two-phase exponential decay after intravenous use. In the initial phase, distribution between intravascular and other compartments (body fluids) occurs with a half-life of elimination from the plasma of 1 to 8 hours. In the subsequent phase the half-life varies between 5 - 18 hours, with an average of about 12 hours. This appears to correspond to the true biological half-life. The incremental recovery of Haemoctin® SDH 250, 500 or 1000 is approximately 0.020 ± 0.003 IU/ml/IU/kg b.w. The level of factor VIII activity after intravenous use of 1 IU factor VIII per kg b.w. is about 2 %. Other pharmacokinetic parameters of Haemoctin®SDH 250, 500 or 1000 are: • Area under the curve (AUC): about 17 IU x h / ml • Mean residence time (MRT): about 15 h • Clearance: about 155 ml/h.		**Pharmacokinetic properties**
Human plasma coagulation factor VIII (from the concentrate) is a normal constituent of the human plasma and acts like the endogenous factor VIII. Single dose toxicity testing is of no relevance since higher doses result in overloading. Repeated dose toxicity testing in animals is impracticable due to the interference with developing antibodies to heterologous protein. Even doses of several times the recommended human dosage per kilogram body weight show no toxic effects on laboratory animals. Since clinical experience provides no hint for tumorigenic and mutagenic effects of human plasma coagulation factor VIII, experimental studies, particularly in heterologous species, are not considered imperative.		**Preclinical safety data**
Haemoctin® SDH 250, 500 or 1000 must not be mixed with other medicinal products.	Haemoctin® SDH 250 should not be mixed with other medicinal products.	**Incompatibilities**
1 package Haemoctin® SDH 250, 500 or 1000 contains: 1 vial with powder (20 ml) out of glass type I acc. to Ph.Eur. (current edition). Freeze-drying stoppers out of halobutyl-caoutchouc, type I acc. to Ph.Eur. (current edition). 1 vial with solvent (5 ml, 10 ml), glass type I acc. to Ph.Eur. (current edition). Injection stoppers out of halobutyl-caoutchouc, type I acc. to Ph.Eur. (current edition). The pack also contains: 1 disposable syringe (5 ml, 10 ml), 1 transfer system with integral filter, ~~one transfer cannula, one filter needle~~ 1 butterfly cannula.	~~Haemoctin® SDH 250 Each pack contains one vial of powder (250 IU), one vial of 5 ml of water for injections, one single-use syringe, one transfer cannula, one filter needle, and one butterfly cannula. *Other pack sizes:* Haemoctin® SDH 500 Each pack contains one vial of powder (500 IU), one vial of 10 ml of water for injections, one single-use syringe, one transfer cannula, one filter needle, and one butterfly cannula. Haemoctin® SDH 1000 Each pack contains one vial of powder (1000 IU), one vial of 10 ml of water for injections, one single-use syringe, one transfer cannula, one filter needle, and one butterfly cannula.~~	**Nature and contents of container**

• Pull off the closure of the packaging of the transfer system pack. (2) With the water bottle standing upright, place the open side of the pack (blue part of the transfer system) onto the water bottle. (3) • Remove the packaging. This exposes the transparent part of the transfer system. • Turn the combination of transfer system and water vial upside down and, with the vial of dry substance standing upright, push the transparent part of the transfer system into the dry substance vial. (4) The vacuum present in the dry substance vial causes the water to run into the vial of product. (5) Unscrew the blue part of the transfer system together with the water vial. (6) Gently rocking the vial with product helps to dissolve the dry substance. Do not shake vigorously, all foaming is to be avoided! **Injection:** Once you have dissolved the dry substance as described above, screw the enclosed syringe with its Luer-Lock connector onto the substrate vial with the transparent part of the transfer system. (7) This will allow you to draw the dissolved preparation easily into the syringe. A separate filter is unnecessary because the transfer system has its own integral filter. Carefully unscrew the bottle with the transparent part of the transfer system and inject the injection preparation slowly intravenously using the enclosed butterfly needle. Injection rate: 2 - 3 ml/minute. After the butterfly needle has been used, it can be made safe with the protective cap.	~~• Remove the double-ended cannula (with blue cuff) from its sterile packaging. The tip of the needle should not be touched during this procedure. The short needle of the double-ended cannula is inserted through the rubber stopper of the vial with water.~~ ~~• The vial with water is now turned upside down and held over the vial of concentrate, which stand upright, and the free needle tip is rapidly introduced through the centre of the stopper of the vial of concentrate. The vacuum in the concentrate vial sucks in the water, which emerges through the lateral outlet of the needle onto the glass wall.~~ ~~• Remove needle and vial of water from the vial of concentrate and rotate so that the lyophilisate is carefully wetted without being distributed on the glass wall. Do not shake vigorously; all foaming is to be avoided! Reconstitution time is10 minutes at the most.~~ *Injection:* ~~• After the concentrate has been dissolved in the manner stated above, the filter needle is inserted through the vial stopper.~~ ~~• Inject air and draw the dissolved concentrate into the syringe.~~ ~~• Remove the syringe and administer the dissolved concentrate by slow intravenous injection. Injection rate: 2 – 3 ml/minute.~~ ~~• Use a filter needle to draw up the dissolved concentrate with each disposable syringe. Do not draw more than one vial of Haemoctin® SDH 250 through one filter needle.~~	**Instructions for use and handling, and disposal**

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.
שינויים שאינם בגדר החמרות סומנו (בעלון) **מודגשים באפור**. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.