נובמבר 2024

רופא/ה, רוקח/ת נכבד/ה,

הנדון: Feiba 1000U (Factor VIII Inhibitor Bypassing Activity)
עדכון בדבר עדכון העלון לרופא והוספת עלון לצרכן

חברת טקדה ישראל בע"מ באה להודיע בזאת על עדכון עלוני התכשיר עבור המינון שבנידון.
התוויות הרשומות לתכשיר זה:

Control of bleeding episodes in haemophilia A patients with Factor VIII Inhibitors and also in patients with acquired Factor VIII Inhibitors.
Control of bleeding in hemophilia B patients with inhibitors, if no other specific treatment is available.

מרכיב פעיל: **Factor VIII Inhibitor Bypassing Activity 1000U/vial**

העלונים העדכניים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם על ידי פניה לחברת טקדה ישראל בע"מ, רח' אפעל 25, פתח תקוה, 03-3733140

בברכה,
טקדה ישראל בע"מ

להלן פירוט השינויים העיקריים בעלון לרופא (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה, טקסט המהווה החמרה מודגש בצהוב):

❖ **עלון לרופא:**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Factor VIII Inhibitor Bypassing Activity

~~(a) Powder: each glass vial contains:~~

~~FEIBA~~	~~1000 U*~~
~~Active ingredient:~~	
~~Human Plasma Protein with a Factor Eight Inhibitor Bypassing Activity of~~	~~400-1200 mg 1000 units~~
~~Other ingredients:~~	
~~Sodium Chloride~~	~~160 mg~~
~~Sodium Citrate dihydrate~~	~~80 mg~~

1 ml of Feiba 1000U contains 50 U* factor VIII inhibitor bypassing activity.
The presentation 1 000 U FEIBA contains 1 000 U factor VIII inhibitor bypassing activity in 400 – 1 200 mg human plasma protein.

~~*) A solution containing 1 U of FEIBA shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma to 50% of the buffer value (blank value).~~

FEIBA also contains the factors II, IX and X mainly in non-activated form as well as activated factor VII; factor VIII ~~coagulant~~ coagulation antigen (F-VIII C:Ag) is present ~~in~~ at a concentration of up to 0.1 U/1 U FEIBA. The factors of the kallikrein-kinin system are present in trace amounts only, if at all.

*1 unit of FEIBA shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma by 50% of the buffer value (blank value).

~~(b) Solvent: each glass vial contains 20 ml sterile water for injections.~~

Excipient~~s~~ with known effect:

FEIBA 1000U contains approximately 80 mg sodium per vial.

For ~~a~~ the full list of excipients, see section 6.1.

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4.5 Interactions with other medicinal products and other forms of interaction

No adequate and well-controlled studies of the combined or sequential use of FEIBA and recombinant Factor VIIa, antifibrinolytics or emicizumab have been conducted. The possibility of thromboembolic events should be considered when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used during treatment with FEIBA. Therefore, antifibrinolytics should not be used for approximately 6 to 12 hours after the administration of FEIBA.
In cases of concomitant rFVIIa use a potential drug interaction cannot be excluded according to available *in vitro* data and clinical observations (potentially resulting in adverse events such as a thromboembolic event).

~~Clinical experience from an emicizumab clinical trial suggests that a potential drug interaction may exist with emicizumab when FEIBA was used as part of a treatment regimen for breakthrough bleeding which may result in thromboembolic events and thrombotic microangiopathy~~During two emicizumab clinical trials, 23 participants receiving emicizumab prophylaxis also received FEIBA for the management of 78 breakthrough bleeds. 59 of the 78 bleeds were managed with an average daily dose ≤ 100 U/kg/day for ≤ 2 days without TMA complications. 19 of the 78 bleeds were managed with > 100 U/kg/day for > 1 day with TMA complication occurring in 3 patients (of whom 2 patients also received rFVIIa for the same bleeding event) ~~(~~see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of FEIBA in pregnant ~~or lactating~~ women. Physicians should balance the potential risks and only prescribe FEIBA if clearly needed, taking into consideration that pregnancy ~~and the postpartum period~~ confers an increased risk of thromboembolic events, and several complications of pregnancy that are associated with an increased risk of DIC.

Breastfeeding
There are no adequate data from the use of FEIBA in lactating women. Physicians should balance the potential risks and only prescribe FEIBA if clearly needed, taking into consideration that the postpartum period confers an increased risk of thromboembolic events.

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4.8 Undesirable effects

Adverse Reactions		
System organ class (SOC)	**Preferred current MedDRA Term**	**Frequency* Category**
Investigations	Drop in blood pressure	Unknown
	Hepatitis B surface antibody positive[c]	Common
	Fibrin D-dimer increased	Unknown

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6.5 Nature and contents of container

Each package contains either:
- 1 vial with FEIBA 1000 U (powder for solution for infusion or injection)
- 1 vial with 20 ml Water for Injections
- 1 disposable syringe (20 ml capacity)
- 1 disposable needle
- 1 butterfly needle ~~with clamp (winged set for injection)~~
- 1 filter needle
- 1 transfer needle
- ~~-~~1 aeration needle
-

or

- 1 vial with FEIBA 1000 U (powder for solution for infusion or injection)
- 1 vial with 20 ml Water for Injections
- 1 ~~Baxject~~ BAXJECT II Hi-Flow ~~– Needleless transfer device intended for transferring and mixing drugs contained in two vials into a syringe~~
- 1 disposable syringe
- 1 disposable needle
- ~~-~~1 butterfly needle ~~with clamp (winged set for injection)~~

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6.6. Special precautions for disposal and other handling

Do not refrigerate after reconstitution.

After complete reconstitution of FEIBA, its injection or infusion should be commenced immediately and must be completed within three hours following reconstitution.

❖ **עלון לצרכן:**

2. לפני השימוש בתרופה

עלייך ליידע את הרופא אם יש לך אלרגיה ידועה כלשהי
עלייך ליידע את הרופא במידה ואתה בדיאטה דלת נתרן

אין להשתמש בתרופה

~~במצבים הבאים~~, יש להשתמש בפייבה במצבים הבאים רק אם – לדוגמה בשל רמת מעכבים גבוהה ביותר – לא צפויה תגובה לטיפול באמצעות הריכוז המתאים של גורם הקרישה:
~~אם קיימות חלופות טיפוליות אחרות:~~

- אם אתה רגיש (אלרגי) לחומר הפעיל או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה (כמפורט בסעיף 6).
- אם קיימת קרישה מפוזרת בתוך כלי הדם (DIC). (DIC היא הפרעה של צריכת גורמי קרישה, מצב מסכן חיים שבו יש קרישת דם עודפת עם היווצרות קרישי דם מרובים בכלי הדם, מה שמוביל בתורו לתצרוכת של גורמי קרישה בכל הגוף).
- ~~במקרים של פקקת חריפה ו/או תסחיף (כולל אוטם שריר הלב).~~

- במקרה של אוטם שריר הלב, פקקת אקוטית ו/או תסחיף יש להשתמש בפייבה רק במצב של דימומים מסכני חיים.

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ילדים ומתבגרים:
הניסון בילדים מתחת לגיל 6 מוגבל; יש להתאים את משטר המינון של מבוגרים למצב הקליני של הילד.

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4. תופעות לוואי

- **תופעות לוואי ששכיחותן אינה ידועה** (שכיחותן איננה יכולה להיקבע מתוך המידע הזמין):

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- **בדיקות**: ירידה בלחץ דם, עלייה ברמת פיברין די-דימר בדם.

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6. מידע נוסף

כל אריזה מכילה:

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The following information is intended for medical or healthcare professionals only:

The treatment is to be initiated and monitored by a physician experienced in the treatment of coagulation disorders.

Posology
Dosage and duration of treatment depend on the severity of the haemostatic disorder, the localization and the extent of the bleeding, as well as the clinical condition of the patient.

Dosage and frequency of administration should always be guided by the clinical efficacy in each individual case.

As a general guideline a dose of 50 - 100 U FEIBA per kg body weight is recommended; a single dose of 100 U/kg body weight and a maximum daily dose of 200 U/kg body weight must not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses.

Due to patient-specific factors the response to a bypassing agent can vary, and in a given bleeding situation patients experiencing insufficient response to one agent may respond to another agent. In case of insufficient response to one bypassing agent, use of another agent should be considered.

Paediatric population
The experience in children under 6 years of age is limited; the same dose regimen as in adults should be adapted to the child's clinical condition.

1) Spontaneous bleeding
Joint, muscle and soft tissue haemorrhage
A dose of 50 - 75 U/kg body weight at 12-hour intervals is recommended for minor to moderately severe bleeding. The treatment is to be continued until a clear improvement of the clinical symptoms, e.g. reduction of pain, decrease of swelling or increase of joint mobility, occurs.

For severe muscle and soft tissue bleeding, e.g., retroperitoneal haemorrhages, a dose of 100 U/kg body weight at 12-hour intervals is recommended.

Mucous membrane haemorrhage
A dose of 50 U/kg body weight every 6 hours under careful monitoring of the patient (visual control of bleeding, repeated determination of haematocrit) is recommended. If the bleeding does not stop, the dose may be increased to 100 U/kg body weight, however a daily dose of 200 U/kg body weight must not be exceeded.

Other severe haemorrhages
In severe haemorrhage, such as CNS bleeding, a dose of 100 U/kg body weight at 12-hour intervals is recommended. In individual cases, FEIBA may be administered at 6-hour intervals, until clear improvement of the clinical condition is achieved. (The maximum daily dose of 200 U/kg body weight must not be exceeded!)

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2) Surgery
In surgical interventions, an initial dose of 100 U/kg body weight may be administered preoperatively, and a further dose of 50 – 100 U/kg body weight may be administered after 6 – 12 hours. As a postoperative maintenance dose, 50 – 100 U/kg body weight may be administered at 6 – 12-hour intervals; dosage, dosage intervals and duration of the peri- and postoperative therapy are guided by the surgical intervention, the patient's general condition and the clinical efficacy in each individual case. (The maximum daily dose of 200 U/kg body weight must not be exceeded!)

3) Use of FEIBA in special patient groups
See also below "Treatment of haemophilia B patients with inhibitors".
In combination with factor VIII concentrate, FEIBA was also used for long term therapy to achieve complete and permanent elimination of the factor VIII inhibitor.

Monitoring
In case of inadequate response to treatment with the product, it is recommended that a platelet count be performed because a sufficient number of functionally intact platelets are considered to be necessary for the efficacy of the product.

Due to the complex mechanism of action, no direct monitoring of active ingredients is available. Coagulation tests such as the whole blood coagulation time (WBCT), the thromboelastogram (TEG, r-value) and the aPTT usually show only little reduction and do not necessarily correlate with the clinical efficacy. Therefore these tests have little significance in the monitoring of the therapy with FEIBA.

Method of administration
FEIBA is to be administered slowly intravenously. An infusion rate of 2 U/kg body weight per minute must not be exceeded.

FEIBA is to be reconstituted immediately prior to administration. The solution should be used immediately (as the preparation does not contain preservatives).

Swirl gently until all material is dissolved. Ensure that FEIBA is completely dissolved; otherwise, less FEIBA Units will pass through the device filter.

After reconstitution, the solution should be inspected for particulate matter and discoloration prior to administration. Do not use solutions which are cloudy or have deposits.

Open containers must not be re-used.

Do not use the product if its sterile barrier has been breached, its package damaged or if it shows signs of deterioration.

Use only the included Water for Injections and the included device set for reconstitution. If devices other than those enclosed are used, ensure the use of an adequate filter with a pore size of at least 149 µm.

Do not refrigerate after reconstitution.

After complete reconstitution of FEIBA, its injection or infusion should be commenced immediately and must be completed within three hours following reconstitution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Therapy monitoring

Individual doses of 100 U/kg body weight and daily doses of 200 U/kg body weight must not be exceeded. Patients receiving 100 U/kg body weight or more must be monitored carefully, particularly for the development of DIC and/or acute coronary ischaemia and for symptoms of other thrombotic or thromboembolic events. High doses of FEIBA should be administered only as long as strictly necessary – in order to stop a haemorrhage.

If clinically significant changes in blood pressure or pulse rate, respiratory distress, coughing or chest pain occur, the infusion is to be discontinued immediately and appropriate diagnostic and therapeutic measures are to be initiated. Significant laboratory parameters for DIC are a drop in fibrinogen, a drop of the thrombocyte count and/or the presence of fibrin/fibrinogen degradation products (FDP). Other parameters for DIC are a clearly prolonged thrombin time, prothrombin time or aPTT. In patients with inhibitor haemophilia or with acquired inhibitors to factors VIII, IX and/or XI, the aPTT is prolonged by the underlying disease.

Administration of FEIBA to patients with inhibitors may result in an initial anamnestic rise in inhibitor levels. Upon continued administration of FEIBA, inhibitors may decrease over time. Clinical and published data suggest that the efficacy of FEIBA is not reduced.

Patients with inhibitor haemophilia or with acquired inhibitors to coagulation factors, who are treated with FEIBA, may have increased bleeding tendency as well as increased risk of thrombosis at the same time.

Laboratory tests and clinical efficacy

In vitro tests, such as aPTT, whole blood coagulation time (WBCT) and thromboelastograms (TEG) as proof of efficacy do not have to correlate with the clinical picture. Therefore, attempts to normalize these values by increasing the dose of FEIBA cannot be successful, and are even to be strongly rejected because of the possible risk of triggering a DIC through overdosing.

Significance of the thrombocyte count

If the response to treatment with FEIBA is inadequate, conducting a thrombocyte count is recommended since a sufficient number of functionally intact thrombocytes is necessary for the efficacy of FEIBA.

Treatment of haemophilia B patients with inhibitors

The experience in haemophilia B patients with factor IX inhibitors is limited due to the rarity of the disease. Five haemophilia B patients with inhibitors were treated with FEIBA during clinical trials either on-demand, prophylactically or for surgical interventions:

In a prospective open-label, randomized, parallel clinical study in haemophilia A or B patients with persistent high-titre inhibitors (090701, PROOF), 36 patients were

randomized to either 12 months ± 14 days of prophylactic or on-demand therapy. The 17 patients in the prophylaxis arm received 85 ± 15 U/kg FEIBA administered every other day and the 19 patients in the on-demand arm were treated individually determined by the physician. Two haemophilia B patients with inhibitors were treated in the on-demand arm and one haemophilia B patient was treated in the prophylactic arm. The median ABR (annualized bleeding rate) for all types of bleeding episodes in patients in the prophylaxis arm (median ABR = 7.9) was less than that of patients in the on-demand arm (median ABR = 28.7), which amounts to a 72.5 % reduction in median ABRs between treatment arms.

In another completed prospective non-interventional surveillance study of the perioperative use of FEIBA (PASS-INT-003, SURF) a total of 34 surgical procedures were performed in 23 patients. The majority of patients (18) were congenital haemophilia A patients with inhibitors, two were haemophilia B patients with inhibitors and three were patients with acquired haemophilia A with inhibitors. The duration of FEIBA exposure ranged from 1 to 28 days, with a mean of 9 days and a median of 8 days. The mean cumulative dose was 88 347 U and the median dose was 59 000 U. For haemophilia B patients with inhibitors, the longest exposure to FEIBA was 21 days and the maximum dose applied was 7 324 U.

In addition, 48 patients in literature are reported when FEIBA was used for treatment and prevention of bleeding episodes in haemophilia B patients with factor IX inhibitor (34 haemophilia B patients with inhibitors were treated on-demand, six haemophilia B patients with inhibitors were treated prophylactically and eight haemophilia B patients with inhibitors were treated for surgical procedures).

There are also isolated reports on the use of FEIBA in the treatment of patients with acquired inhibitors to factors IX, X, XI and XIII.
In rare cases, FEIBA was also used in patients with the presence of von Willebrand factor inhibitor.

Reconstitution of the powder for preparing a solution for injection or infusion with needles:

1. Warm the unopened solvent vial (Water for Injections) to room temperature or max. +37°C if necessary.
2. Remove the protective caps from the powder vial and solvent vial (Fig. A) and disinfect the rubber stoppers of both vials.
3. Open the protective cap from one end of the enclosed transfer needle by twisting, remove it and insert the needle through the rubber stopper of the solvent vial (Fig. B and C).
4. Remove the protective cap from the other end of the transfer needle taking care not to touch the exposed end!
5. Invert the solvent vial and insert the free end of the transfer needle through the rubber stopper of the powder vial (Fig. D). The solvent will be drawn into the powder vial by vacuum.
6. Disconnect the two vials by removing the transfer needle from the powder vial (Fig. E).
   Gently swirl the powder vial to accelerate dissolution.
7. Upon complete reconstitution of the powder, insert the enclosed aeration needle (Fig. F) and any foam will collapse. Remove the aeration needle.

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Infusion/ Injection:

1. Open one end of the protective cap from the enclosed filter needle by twisting, remove it and fit the needle on to the sterile disposable syringe. Draw the solution into the syringe (Fig. G).
2. Disconnect the filter needle from the syringe and slowly administer the solution intravenously with the enclosed infusion set (or the enclosed disposable needle).

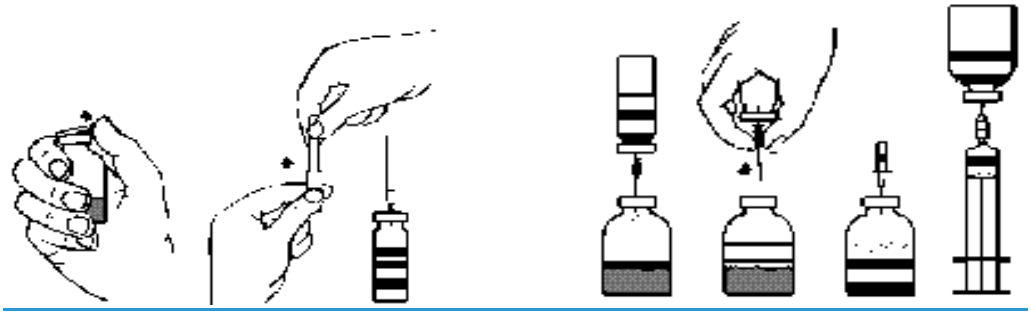

Fig. A Fig. B Fig. C Fig. D Fig. E Fig. F Fig. G

Reconstitution of the powder for preparing a solution for infusion with the BAXJECT II Hi-Flow:

1. Warm the unopened solvent vial (Water for Injections) to room temperature (15 °C to 25 °C), for example by using a water bath for several minutes (max. 37 °C) if necessary.
2. Remove the protective caps from the powder vial and solvent vial and disinfect the rubber stoppers of both vials. Place the vials on an even surface.
3. Open the packaging of the BAXJECT II Hi-Flow by pulling off the protective foil without touching the contents of the package (Fig. a). Do not remove the transfer system from the package at this point.
4. Turn the package around and press the transparent plastic pin through the rubber stopper of the solvent vial (Fig. b). Now remove the packaging from the BAXJECT II Hi-Flow (Fig. c). Do not remove the blue protective cap from the BAXJECT II Hi-Flow.

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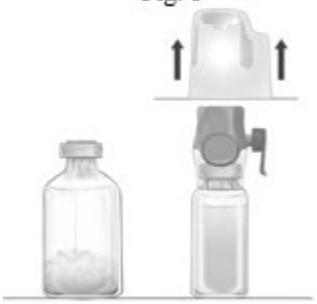
5. Now turn the system, consisting of the BAXJECT II Hi-Flow and the solvent vial, in such a way that the solvent vial is on top. Press the purple pin of the BAXJECT II Hi-Flow through the FEIBA vial. The solvent is drawn into the FEIBA vial by vacuum (Fig. D.).
6. Swirl, but do not shake the entire system gently until the powder is dissolved. Make sure that the FEIBA has been dissolved completely, as active material may otherwise be retained by the filter in the system.

Fig. a

Fig. b

Fig. c



Infusion

1. Remove the blue protective cap from the BAXJECT II Hi-Flow. Tightly connect the syringe to the BAXJECT II Hi-Flow. DO NOT DRAW AIR INTO THE SYRINGE (Fig. e). In order to ensure tight connection between syringe and BAXJECT II Hi-Flow, the use of a luer lock syringe is highly recommended (turn syringe in clockwise direction until stop position when mounting).
2. Invert the system so that the dissolved product is on top. Draw the dissolved product into the syringe by pulling the plunger back SLOWLY and ensure that the tight connection between BAXJECT II Hi-Flow and the syringe is maintained throughout the whole pulling process (Fig. f).
3. Disconnect the syringe.
4. If foaming of the product in the syringe occurs, wait until the foam is collapsed. Slowly administer the solution intravenously with the enclosed infusion set (or disposable needle).

Fig. d

Fig. e

Fig. f

Do not exceed an infusion rate of 2 U FEIBA/kg body weight per minute.

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