# הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 3102.50)

**תאריך** April 19, 2015

**שם תכשיר באנגלית ומספר הרישום** FEIBA NF 500 U, 1000 U_

**Powder for Solution for Injection**

**_Reg No: 500 U: 026 14 25389 00; 1000U: 0261525390 00**

**שם בעל הרישום** Teva Medical (Marketing) Ltd., Haorgim St 8, Ashdod 77100

טופס זה מיועד לפרוט ההחמרות בלבד !

**ההחמרות המבוקשות**

| טקסט חדש | טקסט נוכחי | פרק בעלון |
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| - Control of bleeding episodes in haemophilia A patients with Factor VIII inhibitors and also in patients with acquired Factor VIII inhibitors.<br>- Control of bleeding in hemophilia B patients with inhibitors, if no other specific treatment is available. | FEIBA NF is indicated for the control of bleeding episodes in haemophilia A patients with Factor VIII inhibitors and also in patients with acquired Factor VIII inhibitors. | **Indication** |
| | | **Contraindications** |
| **Surgery**<br>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!)<br>~~**Surgery**~~<br>~~50-100 U/kg bw should be given at intervals of up to 6 hours, a maximum daily dose of 200 U/kg bw should not be exceeded.~~<br>**Use of FEIBA NF in special patient groups**<br>See Section 5.1 for information in relation to hemophilia B patients with factor IX inhibitor.<br>In combination with factor VIII concentrate, NF was also used for long term therapy to achieve complete and permanent elimination of the factor VIII inhibitor. | **Surgery**<br>50-100 U/kg bw should be given at intervals of up to 6 hours, a maximum daily dose of 200 U/kg bw should not be exceeded. | **Posology, dosage & administration** |
| Hypersensitivity Reactions<br>FEIBA NF can precipitate allergic-type hypersensitivity reactions that have included, urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension; | **Risk of Thrombotic and Thromboembolic Events**<br>Thrombotic and thromboembolic events, including disseminated intravascular coagulation (DIC), venous thrombosis, | **Special Warnings and Special Precautions for Use** |

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| these reactions can be severe and can be systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported.<br><br>Patients should be informed of the early signs of hypersensitivity reactions, for example erythema, skin rash, generalized urticaria, pruritus, breathing difficulties/dyspnoea, tightness of the chest, general indisposition, dizziness and drop in blood pressure up to allergic shock.<br>At the first sign or symptom of an infusion/hypersensitivity reaction, FEIBA NF administration should be stopped and medical care initiated as appropriate.<br>When considering re-exposure to FEIBA NF in patients with suspected hypersensitivity to the product or any of its components, the expected benefit and the risk of re-exposure must be carefully weighed, taking into account the known or suspected type of the patient's hypersensitivity (allergic or non-allergic), including potential remedial and/or preventative therapy or alternative therapeutic agents.<br><br>Thromboembolic Events<br><br>Thromboembolic events, including disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, have occurred in the course of treatment with FEIBA NF. Some of these events occurred with doses above 200 U/kg/day or in patients with other risk factors (including DIC, advanced atherosclerotic disease, crush injury or septicemia) for thromboembolic events. Concomitant treatment with recombinant Factor Vlla may increase the risk of developing a thromboembolic event.<br>The possible presence of such risk factors should always be considered in patients with congenital and acquired hemophilia.<br>FEIBA NF should be used with particular caution and only if there are no therapeutic alternatives in patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, DIC, arterial or venous thrombosis, post-operative immobilization, elderly patients and neonates.<br>If signs or symptoms of thrombotic and thromboembolic events are observed, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.<br><br>A single dose of 100 U/kg body weight and a daily dose of 200 U/kg body weight should not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses. When used to stop bleeding, the product should be given only for as long as absolutely necessary to achieve the therapeutic goal.<br><br>Therapy monitoring<br><br>Individual doses of 100 U/kg body weight and daily | pulmonary embolism, myocardial infarction, and stroke, have occurred in the course of treatment with FEIBA NF.<br><br>The risk of thrombotic and thromboembolic events may be increased with high doses of FEIBA NF. Some of these events occurred with doses above 200 U/kg/day or in patients with other risk factors for thromboembolic events. The possible presence of such risk factors should always be considered in patients with congenital and acquired hemophilia.<br>A single dose of 100 U/kg body weight and a daily dose of 200 U/kg body weight should not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses. Patients receiving more than 100 U/kg body weight must be monitored for the development of DIC and/or acute coronary ischemia. When used to stop bleeding, the product should be given only for as long as absolutely necessary to achieve the therapeutic goal.<br><br>In the following situations FEIBA NF should only be used when no reaction to treatment with other appropriate coagulation factor concentrates is to be expected- such as in case of a high inhibitor titre and a life-threatening haemorrhage or risk of bleeding e.g. posttraumatic or postoperative.<br><br>Disseminated Intravascular Coagulation (DIC):<br><br>Liver damage<br>Due to the delayed clearance of activated coagulation factors, patients with impaired liver function are at increased risk of developing DIC.<br><br>Coronary heart disease, acute thrombosis and/or embolism.<br><br>**Allergic-Type Hypersensitivity Reactions**<br><br>As with any intravenously administered plasma products, allergic type hypersensitivity reactions may occur. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, drop in blood pressure and anaphylactic shock. If these symptoms occur, patients should be advised to discontinue the treatment and to contact their physician immediately. Shock is treated according to the rules of | |

doses of 200 U/kg body weight must not be exceeded. Patients receiving more than 100 U/kg body weight must be monitored for the development of DIC and/or acute coronary ischemia.. High doses of FEIBA NF should be administered only as long as strictly necessary – in order to stop a hemorrhage.

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 hemophilia or with acquired inhibitors to factors VIII, IX and/or XI, the aPTT is prolonged by the underlying disease.

Patients with inhibitor hemophilia or with acquired inhibitors to coagulation factors, who are treated with FEIBA NF, 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 NF 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 NF is inadequate, conducting a thrombocyte count is recommended since a sufficient number of functionally intact thrombocytes is necessary for the efficacy of FEIBA NF.

PRECAUTIONS

Thromboembolic Complications

In the following situations, FEIBA NF is to be applied only if no reaction to treatment with suitable blood coagulation factor concentrates can be expected – e.g. in case of a high inhibitor titer and a life-threatening hemorrhage or risk of bleeding (e.g. post-traumatically or postoperatively):

- Disseminated intravascular coagulation (DIC): laboratory findings and/or clinical symptoms
- Liver damage: Due to the delayed clearance of activated coagulation factors, patients with impaired liver function are at increased risk of developing DIC.
- Coronary heart disease, acute thrombosis and/or embolism.

modern shock therapy.

When considering re-exposure to FEIBA NF in patients with suspected hypersensitivity to the product or any of its components, the expected benefit and the risk of re-exposure must be carefully weighed, taking into account the known or suspected type of the patient's hypersensitivity (allergic or non-allergic), including potential remedial and/or preventative therapy or alternative therapeutic agents.

In patients with a history of hypersensitivity reactions to plasma derivatives the prophylactic administration of antihistamines may be indicated.

**Appropriate vaccination should be considered in patients with an inhibitor against a coagulation factor.**

**As the quantity of sodium in the maximum daily dose may exceed 200 mg, special care should be taken with individuals on a low sodium diet.**

**Monitoring of Therapy**
Individual doses of 100 U/kg body weight and daily doses of 200 U/kg body weight must not be exceeded. Patients who receive an individual dose of 100 U/kg body weight are to be monitored carefully, particularly with regard to the development of a DIC or the occurrence of symptoms of acute coronary ischaemia. High doses of FEIBA NFshould be administered only as long as strictly necessary 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. Laboratory parameters indicative at DIC are decreased fibrinogen values, decreased platelet count and/or the presence of fibrin/fibrinogen degradation products (FDP).

Other parameters of DIC include significantly prolonged thrombin time, prothrombin time, or aPTT.
If coagulation parameters are suspicious of DIC, a physician experienced in coagulation therapies should be consulted.

There is insufficient data in children under 6 years of age to recommend the use of FEIBA NF. However, inhibitor

Patients who receive FEIBA NF should be monitored for the development of DIC, acute coronary ischemia, and signs and symptoms of other thromboembolic events. At the first signs or symptoms of thrombotic and thromboembolic events, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.

Discordant Response to Bypassing Agents

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.

Anamnestic Responses

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

Hepatitis B Surface Antibodies and Test Interpretation

After administration of high doses of FEIBA NF, the transitory rise of passively transferred Hepatitis B surface antibodies may result in misleading interpretation of positive results in serological testing.

Pediatrics

Case reports and limited clinical trial data suggest that FEIBA NF can be used in children younger than 6 years of age. The same dose regimen as in adults should be adapted to the child's clinical condition.

Prophylactic use in hemophilia B patients with inhibitors

Due to the rarity of the disease, only limited clinical data is available for the prophylaxis of bleeding in hemophilia B patients (literature case reports, n = 4, and clinical data in prophylaxis study 090701, n = 1).

Transmission of infectious agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation / removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective

formation is a common occurrence in haemophilic children undergoing factor VIII replacement therapy. Case studies have shown the successful use of FEIBA NF in the young age group.

FEIBA NF 500 U and FEIBA NF 1000 U contain approx. 80 mg sodium (calculated) per vial. This has to be attended for patients on low sodium diet.

**Acquired haemophilia**
Patients with inhibitor haemophilia or with acquired inhibitors to coagulation factors, who are treated with FEIBA NF, 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 clotting time (WBCT) and thromboelastograms (TEG) as proof of efficacy do not have to correlate with the clinical picture. Therefore, attempts to normalise these values by increasing the dose of FEIBA NF cannot be successful, and are even to be strongly rejected because of the possible risk of triggering a DIC through overdosing.

**Significance of Platelet Count**
In case of inadequate response to treatment with FEIBA NF it is recommended to perform a platelet count, since a sufficient number of functionally intact platelets are considered necessary for the efficacy of FEIBA NF.

**Measures to prevent transmission of infectious agents**
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific makers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.
The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped virus hepatitis A virus (HAV) and Parvovirus B19.

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| agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.<br>The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).<br><br>It is strongly recommended that every time that FEIBA NF is administered to the patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.<br>Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/ repeated receipt of human plasma-derived products including FEIBA NF.<br><br>Excipient related considerations<br><br>FEIBA NF contains approximately 4 mg sodium (calculated) per ml; it is approx. 80 mg sodium for the presentation 500 U and 1000 U FEIBA NF. This is to be taken into consideration in patients on a low sodium diet.<br><br>~~**Risk of Thrombotic and Thromboembolic Events**~~<br><br>~~Thrombotic and thromboembolic events, including disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, have occurred in the course of treatment with FEIBA NF.~~<br>~~The risk of thrombotic and thromboembolic events may be increased with high doses of FEIBA NF. Some of these events occurred with doses above 200 U/kg/day or in patients with other risk factors for thromboembolic events. The possible presence of such risk factors should always be considered in patients with congenital and acquired hemophilia.~~<br>~~A single dose of 100 U/kg body weight and a daily dose of 200 U/kg body weight should not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses. Patients receiving more than 100 U/kg body weight must be monitored for the development of DIC and/or acute coronary ischemia. When used to stop bleeding, the product should be given only for as long as absolutely necessary to achieve the therapeutic goal.~~<br><br>~~In the following situations FEIBA NF should only be used when no reaction to treatment with other appropriate coagulation factor concentrates is to be expected such as in case of a high inhibitor titre and a life threatening haemorrhage or risk of bleeding e.g. posttraumatic or postoperative.~~<br><br>~~Disseminated Intravascular Coagulation (DIC):~~ | Appropriate vaccination (against hepatitis A and B) should be considered for patients in regular/repeated receipt of plasma-derived products including FEIBA NF.<br><br>In the interest of patients, it is strongly recommended that name and batch number of the product be recorded every time FEIBA is administered in order to be able to link patient and product batch.<br><br>**Other Precautions**<br><br>Discordant Response to Bypassing Agents<br>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.<br><br>Anamnestic Responses<br>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.<br><br>Clinical and published data suggest that the efficacy of FEIBA is not reduced.<br><br>Hepatitis B Surface Antibodies and Test Interpretation<br><br>After administration of high doses of FEIBA, the transitory rise of passively transferred Hepatitis B surface antibodies may result in misleading interpretation of positive results in serological testing.<br><br>Prophylactic use<br>Only limited clinical data is available on the application of FEIBA for the prophylaxis of bleeding in hemophilia patients.<br><br>Pediatrics<br>Case reports and limited clinical trial data suggest that FEIBA can be used in children younger than 6 years of age. | |

Liver damage
Due to the delayed clearance of activated coagulation factors, patients with impaired liver function are at increased risk of developing DIC.

Coronary heart disease, acute thrombosis and/or embolism.

**Allergic-Type Hypersensitivity Reactions**

As with any intravenously administered plasma products, allergic type hypersensitivity reactions may occur. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, drop in blood pressure and anaphylactic shock. If these symptoms occur, patients should be advised to discontinue the treatment and to contact their physician immediately. Shock is treated according to the rules of modern shock therapy.

When considering re-exposure to FEIBA NF in patients with suspected hypersensitivity to the product or any of its components, the expected benefit and the risk of re-exposure must be carefully weighed, taking into account the known or suspected type of the patient's hypersensitivity (allergic or non allergic), including potential remedial and/or preventative therapy or alternative therapeutic agents.

In patients with a history of hypersensitivity reactions to plasma derivatives the prophylactic administration of antihistamines may be indicated.

**Appropriate vaccination should be considered in patients with an inhibitor against a coagulation factor.**

**As the quantity of sodium in the maximum daily dose may exceed 200 mg, special care should be taken with individuals on a low sodium diet.**

**Monitoring of Therapy**
Individual doses of 100 U/kg body weight and daily doses of 200 U/kg body weight must not be exceeded. Patients who receive an individual dose of 100 U/kg body weight are to be monitored carefully, particularly with regard to the development of a DIC or the occurrence of symptoms of acute coronary ischaemia. High doses of FEIBA NFshould be administered only as long as strictly necessary 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. Laboratory parameters indicative at DIC are decreased fibrinogen values, decreased platelet count and/or the presence of fibrin/fibrinogen degradation products (FDP).

Other parameters of DIC include significantly

prolonged thrombin time, prothrombin time, or aPTT.
If coagulation parameters are suspicious of DIC, a physician experienced in coagulation therapies should be consulted.

There is insufficient data in children under 6 years of age to recommend the use of FEIBA NF. However, inhibitor formation is a common occurrence in haemophilic children undergoing factor VIII replacement therapy. Case studies have shown the successful use of FEIBA NF in the young age group.

FEIBA NF 500 U and FEIBA NF 1000 U contain approx. 80 mg sodium (calculated) per vial. This has to be attended for patients on low sodium diet.

**Acquired haemophilia**
Patients with inhibitor haemophilia or with acquired inhibitors to coagulation factors, who are treated with FEIBA NF, 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 clotting time (WBCT) and thromboelastograms (TEG) as proof of efficacy do not have to correlate with the clinical picture. Therefore, attempts to normalise these values by increasing the dose of FEIBA NF cannot be successful, and are even to be strongly rejected because of the possible risk of triggering a DIC through overdosing.

**Significance of Platelet Count**
In case of inadequate response to treatment with FEIBA NF it is recommended to perform a platelet count, since a sufficient number of functionally intact platelets are considered necessary for the efficacy of FEIBA NF.

**Measures to prevent transmission of infectious agents**
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific makers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.
The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non enveloped virus hepatitis A virus (HAV) and Parvovirus B19.

Appropriate vaccination (against hepatitis A and B) should be considered for patients in regular/repeated receipt of plasma derived products including FEIBA NF.

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| In the interest of patients, it is strongly recommended that name and batch number of the product be recorded every time FEIBA is administered in order to be able to link patient and product batch.<br><br>**Other Precautions**<br><br>Discordant Response to Bypassing Agents<br>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.<br><br>Anamnestic Responses<br>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.<br><br>Hepatitis B Surface Antibodies and Test Interpretation<br><br>After administration of high doses of FEIBA, the transitory rise of passively transferred Hepatitis B surface antibodies may result in misleading interpretation of positive results in serological testing.<br><br>Prophylactic use<br>Only limited clinical data is available on the application of FEIBA for the prophylaxis of bleeding in hemophilia patients.<br><br>Pediatrics<br>Case reports and limited clinical trial data suggest that FEIBA can be used in children younger than 6 years of age. | | |
| No adequate and well-controlled studies of the combined or sequential use of FEIBA NF and recombinant Factor VIIa or antifibrinolytics 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 NF. Therefore, antifibrinolytics should not be used for approximately 6 to 12 hours after the administration of FEIBA NF.<br>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 thromboembolic event).<br><br>It is not recommended to use antifibrinolytics such as epsilon-aminocaproic acid in combination with FEIBA NF.<br><br>If treatment with both antifibrinolytics such as epsilon-aminocaproic acid and FEIBA NF is indicated, the two products should be administered | It is not recommended to use antifibrinolytics such as epsilon-aminocaproic acid in combination with FEIBA NF.<br><br>If treatment with both antifibrinolytics such as epsilon-aminocaproic acid and FEIBA NF is indicated, the two products should be administered at least 6 hours apart. | **Interaction with Other Medicaments and Other Forms of Interaction** |

~~at least 6 hours apart.~~

**Fertility, Pregnancy and Lactation**

FEIBA NF has no, or negligible, influence on the ability to drive or to use machines.

~~No effects of FEIBA NF on the ability to drive and operate machinery have been observed.~~

No effects of FEIBA NF on the ability to drive and operate machinery have been observed.

**Effects on ability to drive and use machines**

The adverse reactions presented in this section have been reported from post marketing surveillance as well as from 2 studies with FEIBA NF for the treatment of bleeding episodes in pediatric and adult patients with hemophilia A or B and inhibitors to factors VIII or IX. One study also enrolled acquired hemophilia patients with factor VIII inhibitors (2 of 49 patients). The adverse reactions from a third study comparing prophylaxis with on-demand treatment have been added.

Frequency categories are defined according t the following convention:

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| 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 |
| unknown | cannot be estimated from the available data |

**Adverse Reactions**

| System organ class (SOC) | Preferred MedDRA (version 15.1) Term | Frequency* Category |
|---|---|---|
| Blood and lymphatic system disorders | Disseminated intravascular coagulation (DIC)<br>Increase of inhibitor titer (anamnestic response)[a] | Unknown<br>Unknown |
| Immune system disorders | Hypersensitivity [c]<br>Urticaria<br>Anaphylactic reaction | Common<br>Unknown<br>Unknown |
| Nervous system disorders | Paresthesia<br>Hypaesthesia<br>Thrombotic stroke<br>Embolic stroke<br>Headache[c]<br>Somnolence<br>Dizziness[b]<br>Dysgeusia | Unknown<br>Unknown<br>Unknown<br>Unknown<br>Commonn<br>Unknown<br>Common<br>Unknown |
| Cardiac disorders | Cardiac infarction<br>Tachycardia | Unknown<br>Unknown |
| Vascular disorders | Thrombosis, Venous | Unknown<br>Unknown |

Following adverse reactions have been reported within the framework of either post marketing surveillance or clinical trials. The frequency cannot be estimated due to the nature of the data and therefore is categorized as unknown:

**Adverse events**

| System organ classes according to MedDRA | Preferred MedDRA term | |
|---|---|---|
| Blood and lymphatic system disorders | Disseminated intravascular coagulation (DIC)<br>Increase of inhibitor titer (anamnestic response[a] | |
| Immune system disorders | Hypersensitivity<br>Urticaria<br>Anaphylactic reaction | |
| Nervous system disorders | Paraesthesia<br>Hypoaesthesia<br>Thrombotic stroke<br>Embolic stroke<br>Headache<br>Somnolence<br>Dizziness<br>Dysgeusia | |
| Cardiac disorders | Myocardial infarction<br>Tachycardia | |
| Vascular disorders | Arterial and venous thrombosis<br>Hypotension<br>Hypertension<br>Flushing | |
| Respiratory, Thoracic, and Mediastinal | Pulmonary embolism<br>Bronchospasm | |

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| | thrombosis<br>Arterial thrombosis<br>Embolism (thromboembolic complications)<br>Hypotension[c]<br>Hypertension<br>Flushing | Unknown<br>Unknown<br>Common<br>Unknown<br>Unknown |
| Respiratory, Thoracic, and Mediastinal disorders | Pulmonary embolism<br>Bronchospasm<br>Wheezing<br>Cough<br>Dyspnea | Unknown<br>Unknown<br>Unknown<br>Unknown<br>Unknown |
| Gastrointestinal disorders | Vomiting<br>Diarrhea<br>Abdominal discomfort<br>Nausea | Unknown<br>Unknown<br>Unknown<br>Unknown |
| Skin and subcutaneous tissue disorders | Sensation of numbness in the face<br>Angioedema<br>Urticaria<br>Pruritus<br>Rash[c] | Unknown<br>Unknown<br>Unknown<br>Unknown<br>Common |
| General disorders and administration site conditions | Pain at the injection site<br>Malaise<br>Feeling hot<br>Chills<br>Pyrexia<br>Chest pain<br>Chest discomfort | Unknown<br>Unknown<br>Unknown<br>Unknown<br>Unknown<br>Unknown<br>Unknown |
| Investigations | Drop in blood pressure<br>Hepatitis B surface antibody positive[c] | Unknown<br>Common |

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| | disorders | Wheezing<br>Cough<br>Dyspnea |
| | Gastrointestinal disorders | Vomiting<br>Diarrhea<br>Abdominal discomfort<br>Nausea |
| | Skin and subcutaneous tissue disorders | Hypoaesthesia facial<br>Angioedema<br>Urticaria<br>Pruritus<br>Rash |
| | General disorders and administration site conditions (Disorders during injection) | Injection site pain<br>Malaise<br>Feeling hot<br>Chills<br>Pyrexia<br>Chest pain<br>Chest discomfort |
| | Investigations | Blood pressure decreased |

[a] Increase of inhibitor titer (anamnestic response) [not a MedDRA PT] is the rise of previously existing inhibitor titers occurring after the administration of FEIBA NF. See Special Warnings and Special Precautions for Use.

A precise estimate of the rate of these adverse reactions not possible from the available data.
ncrease of inhibitor titer (anamnestic response) [not a edDRA PT] is the rise of previously existing inhibitor ers occurring after the administration of FEIBA NF. e Section 4.4.
ADR reported in the original and prophylaxis studies. equency shown is from the prophylaxis study only.
ADR reported in the prophylaxis study. Frequency own is from the prophylaxis study

Class Reactions
Other symptoms of hypersensitivity reactions to plasma-derived products include lethargy and restlessness.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of FEIBA NF is important. It allows continued monitoring of the benefit/risk balance of FEIBA NF. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form

(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il ) or by email (adr@MOH.HEALTH.GOV.IL ).

| **System organ classes according to MedDRA** | **Preferred MedDRA term** | |
|---|---|---|
| Blood and lymphatic system disorders | Disseminated intravascular coagulation (DIC)<br>Increase of inhibitor titer (anamnestic response[a] | |
| Immune system disorders | Hypersensitivity<br>Urticaria<br>Anaphylactic reaction | |
| Nervous system disorders | Paraesthesia<br>Hypoaesthesia<br>Thrombotic stroke<br>Embolic stroke<br>Headache<br>Somnolence<br>Dizziness<br>Dysgeusia | |
| Cardiac disorders | Myocardial infarction<br>Tachycardia | |
| Vascular disorders | Arterial and venous thrombosis<br>Hypotension<br>Hypertension<br>Flushing | |
| Respiratory, Thoracic, and Mediastinal disorders | Pulmonary embolism<br>Bronchospasm<br>Wheezing<br>Cough<br>Dyspnea | |
| Gastrointestinal disorders | Vomiting<br>Diarrhea<br>Abdominal discomfort<br>Nausea | |
| Skin and subcutaneous tissue disorders | Hypoaesthesia facial<br>Angioedema | |

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| | Urticaria<br>Pruritus<br>Rash | | | | | |
| General disorders and administration site conditions (Disorders during injection) | Injection site pain<br>Malaise<br>Feeling hot<br>Chills<br>Pyrexia<br>Chest pain<br>Chest discomfort | | | | | |
| Investigations | Blood pressure decreased | | | | | |

[a] Increase of inhibitor titer (anamnestic response) [not a MedDRA PT] is the rise of previously existing inhibitor titers occurring after the administration of FEIBA NF. See Special Warnings and Special Precautions for Use.

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| | | **Overdosage** |
| Pharmacodynamic properties<br><br>Pharmacotherapeutic group: blood coagulation factors, **ATC code:** B02BD03.<br><br>Although FEIBA NF was developed in the early seventies and its factor VIII inhibitor bypassing activity has been proven in vitro as well as in vivo, its mode of action is still the subject of scientific discussion. FEIBA NF, as found with activity assays, is composed of prothrombin complex zymogens which are both procoagulant (prothrombin FVII, FIX, FX) and anticoagulant (protein C) in relatively equal quantities to the arbitrary FEIBA NF potency unit but its procoagulant enzyme content is relatively low. FEIBA NF, thus, contains the proenzymes of the prothrombin complex factors, but only very small amounts of their activation products, with the contents of FVIIa being the highest. [Turecek PL and Schwarz HP. Chapter 4: Factor Eight Inhibitor Bypassing Activity, in Production of Plasma Proteins for Therapeutic Use, eds. Joseph Bertolini, Neil Goss, John Curling, Wiley 2013, ISBN: 978-0-470-92431-0].<br><br>Current scientific works point to the role of specific components of the activated prothrombin complex, prothrombin (F II) and activated factor X (FXa) in the mode of action of FEIBA NF. [Turecek PL, Varadi K, Gritsch H, et al. Factor Xa and Prothrombin: Mechanism of Action of FEIBA NF. Vox Sang. 77: 72-79, 1999]<br>FEIBA NF controls bleeding by induction and facilitation of thrombin generation, a process for which the formation of the prothrombinase-complex is crucial. A number of biochemical in vitro and in vivo studies have shown that FXa and prothrombin play a critical role in the activity of FEIBA NF. The prothrombinase complex has been found to be a major target site for FEIBA NF. Apart from prothrombin and FXa, FEIBA NF contains other proteins of the prothrombin complex, which could also facilitate haemostasis in haemophilia patients with inhibitors.<br><br>Treatment of hemophilia B patients with inhibitors<br>The experience in hemophilia B patients with factor IX inhibitors is limited due to the rarity of the disease. Five hemophilia B patients with inhibitors were treated with FEIBA NF during clinical trials either on-demand, prophylactically or for surgical interventions: | Pharmacotherapeutic group: Activated prothrombin complex against factor VIII antibody,<br>**ATC Code**: B02BD03<br><br>***Pharmacodynamic properties***<br><br>Although FEIBA was developed in the early 1970s and its factor VIII inhibitor bypassing activity has been demonstrated both in vitro and in vivo, its active principle is still the subject of scientific debate. However, recent scientific work indicates a role of specific components of the activated prothrombin complex, zymogen prothrombin (F II) and activated Factor X (FXa), in the FEIBA NF mode of action.<br><br>***Pharmacokinetic properties***<br><br>Since FEIBA NF is composed of different coagulation factors with varying half-lives for the single components, it is not possible to make any definite statement with regard to the pharmacokinetic properties of FEIBA NF. | **Pharmacological properties** |

In a prospective open-label, randomized, parallel clinical study in hemophilia A or B patients with persistent high-titer 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 NF administered every other day and the 19 patients in the on-demand arm were treated individually determined by the physician. Two hemophilia B patients with inhibitors were treated in the on-demand arm and one hemophilia 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 NF (PASS-INT-003, SURF) a total of 34 surgical procedures were performed in 23 patients. The majority of patients (18) were congenital hemophilia A patients with inhibitors, two were hemophilia B patients with inhibitors and three were patients with acquired hemophilia A with inhibitors. The duration of FEIBA NF 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 hemophilia B patients with inhibitors, the longest exposure to FEIBA NF was 21 days and the maximum dose applied was 7324 U.

In addition 36 case reports are available when FEIBA NF was used for treatment and prevention of bleeding episodes in hemophilia B patients with factor IX inhibitor (24 hemophilia B patients with inhibitors were treated on-demand, four hemophilia B patients with inhibitors were treated prophylactically and eight hemophilia B patients with inhibitors were treated for surgical procedures).

There are also isolated reports on the use of FEIBA NF in the treatment of patients with acquired inhibitors to factors X, XI and XIII.

**Pharmacokinetic properties**

As the mode of action of FEIBA NF is still being discussed, it is not possible to make a conclusive statement about the pharmacokinetic properties.

~~Pharmacotherapeutic group: Activated prothrombin complex against factor VIII antibody,~~
~~**ATC Code**: B02BD03~~

~~***Pharmacodynamic properties***~~

~~Although FEIBA was developed in the early 1970s and its factor VIII inhibitor bypassing activity has been demonstrated both in vitro and in vivo, its active principle is still the subject of scientific debate. However, recent scientific work indicates a role of specific components of the activated prothrombin complex, zymogen prothrombin (F II) and activated Factor X (FXa), in the FEIBA NF mode of action.~~

~~***Pharmacokinetic properties***~~

~~Since FEIBA NF is composed of different coagulation factors with varying half lives for the single components, it is not possible to make any definite statement with regard to the pharmacokinetic properties of FEIBA NF.~~

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| | | **Preclinical Safety Data** |