PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

IMMUNINE® VH

Factor IX Concentrate (Human)

Sterile Powder for solution,
480-720 IU[1]/5 mL, for intravenous injection

Pharmacopeial

ATC code: B02BD04

Hemostatic

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[1] IU based on the 1st International Standard for Human Blood Coagulation Factors II, IX, and X in Concentrates, Code 84/681.

RECENT MAJOR LABEL CHANGES

All Sections – Conversion to June 2017 Template	Jan, 2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

IMMUNINE VH, Factor IX Concentrate (Human) is indicated for:

- Therapy and prophylaxis of bleeding episodes caused by congenital or acquired factor IX deficiency.

1.1 Pediatrics

There is limited data available in children.

1.2 Geriatrics (>65 years of age)

There is no data available to determine whether subjects aged 65 and over respond differently from younger subjects.

2 CONTRAINDICATIONS

IMMUNINE VH is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

IMMUNINE VH must not be used in the following situations if therapeutic alternatives are available:

- Known allergy to heparin or history of heparin induced thrombocytopenia.
- Disseminated intravascular coagulation (DIC) and/or hyperfibrinolysis. Following interruption of these processes by suitable means IMMUNINE VH, Factor IX Concentrate (Human), should only be given for the management of life- threatening bleeding.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia.
- The dosage and duration of treatment depend on the severity of factor IX deficiency, the location and extent of the bleeding, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening hemorrhages.

  Inhibitors

- 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 hemophilia (See Warnings and Precautions).
- In patients with inhibitor titers refractory to higher doses, the use of recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC) preparations should be considered.

3.2 Recommended Dose and Dosage Adjustment

I. Hemophilia B

For the calculation of the factor IX plasma levels as specified below it is assumed that one IU of IMMUNINE VH, Factor IX Concentrate (Human), per kg body weight increases the factor IX plasma level by approximately 0.8 %.

Considering the patient's pre-infusion factor IX plasma level, the required dosage is administered using the following formula:

IMMUNINE VH dose (in IU F IX) = body weight (in kg) x desired increase in F IX (in%) x 1.21U/kg

Regular determinations of the patient's factor IX plasma level are necessary for monitoring the course of therapy and calculation of appropriate maintenance doses.

1. Hemorrhages and Surgery

The following table indicates which factor IX plasma levels are necessary for the management of hemorrhages or for surgical prophylaxis and how long these levels need to be maintained:

Types of hemorrhage or surgical intervention	Therapeutically necessary F IX plasma level (% of normal)	Period during which it is necessary to maintain this F IX plasma level
Minor, e.g.: hemorrhages into joints	30%	At least 1 day, depending on the severity of the hemorrhage

Major, e.g.: hemorrhages into muscles, hemorrhages into the oral cavity, mild trauma capitis, tooth extractions, surgical interventions with low risk of hemorrhage	30 – 50%	3 -4 days, or until absorption of tissue hemorrhage or adequate wound healing
Life-threatening, e.g.: gastro-intestinal, intracranial, intraabdominal, or intrathoracic hemorrhages, fractions, major surgical interventions with high risk of hemorrhage	50 – 70%	After 7 days factor IX levels may be lowered, but therapy should be continued for at least another 7 days or until absorption of hemorrhage or adequate wound healing

In general, IMMUNINE VH is given every 24 hours, corresponding to the biological half-life of factor IX. For surgical prophylaxis the initial dose should be administered one hour prior to surgery. In the case of major surgical interventions, 12-hour treatment intervals should be maintained during the first post-operative days.

1. Prophylactic maintenance therapy

In prophylactic maintenance therapy of severe hemophilia B, a dosage of 20-30 IU/kg body weight twice per week was shown to be effective

Prophylactic dosage regimens should, however, be tailored to individual needs, and the decision on the need and dosage for prophylaxis should thus be made by the treating physician.

II. Hemophiliacs with inhibitor to factor IX

Replacement therapy with human blood coagulation factor IX is usually effective only in low responder patients with an inhibitor titer of less than 10 Bethesda Units. Since the response to human blood coagulation factor IX depends on the patient's inhibitor titer, factor IX levels must be monitored frequently and the dose adjusted accordingly.

In high responder inhibitor patients, other therapeutic measures may be needed.

3.3 Administration

The product should be administered via the intravenous route.

It is recommended not to administer at a rate exceeding 2 mL per minute.

It is strongly recommended that every time that IMMUNINE VH is administered to a 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.

For intravenous injection:

1. After reconstituting the concentrate as described under "Reconstitution", attach the enclosed filter needle to a sterile disposable syringe. Insert filter needle through the concentrate bottle stopper.

2. Inject air and withdraw solution into the syringe.

3. Remove and discard the filter needle. Attach a suitable intravenous needle or winged infusion set and inject solution intravenously (maximum rate 2 mL/min).

For intravenous infusion:

1. After reconstituting the concentrate as described under "Reconstitution", attach the enclosed filter needle to a sterile disposable syringe. Insert filter needle through the concentrate bottle stopper.

2. Inject air and withdraw solution into the syringe.

3. Remove and discard the filter needle. Attach a suitable intravenous needle or winged infusion set and inject solution intravenously (maximum rate 2 mL/min).

Infusion:

If administered by infusion, a disposable infusion set with adequate filter is to be used (maximum rate of infusion: 2 mL/min).

3.4 Reconstitution

Table - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
5 mL	5 mL	5 mL	480-720 IU/5 mL

IMMUNINE VH, Factor IX Concentrate (Human), is to be reconstituted only immediately before application. The solution should then be used promptly (the preparation does not contain any preservative). Any unused solution must be discarded. For reconstitution proceed as follows using aseptic technique:

1. Warm the unopened bottle containing Sterile Water for Injection (diluent) to room temperature (not above 37°C [98°F]).

2. Remove caps from the concentrate and diluent bottles to expose central portions of the rubber stoppers. Cleanse exposed surface of the rubber stoppers with germicidal solution and allow to dry.

3. Remove protective covering from one end of the transfer needle by twisting and pulling. Insert the exposed end through the diluent bottle stopper.

4. Remove protective covering from the other end of the transfer needle taking care not to touch the exposed end. Invert diluent bottle over the concentrate bottle and insert the free end of the transfer needle through the concentrate bottle stopper. Diluent will be drawn into the concentrate bottle by vacuum.

5. Disconnect the two bottles by removing the needle from the concentrate bottle stopper. Gently agitate or rotate the concentrate bottle until all material is dissolved.

Do not refrigerate after reconstitution.

3.5 Missed Dose

Not applicable.

4 OVERDOSAGE

Based on experience with conventional prothrombin complex preparations, overdosage of Factor IX concentrates may result in an increased risk of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism (see "PRECAUTIONS" for measures to be taken).

No symptoms of overdosage with purified FIX have been identified in humans. Therefore, the effects of higher than recommended doses of IMMUNINE VH have not been characterized.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Powder for solution for injection or infusion. Supplied with 5 mL solvent. Factor IX Concentrate (Human), 480 -720 IU[1]/5 mL	Factor II, VII and X (<0.02 IU / 1 IU factor IX), Sodium Chloride, Sodium Citrate, and Tween 80.

IMMUNINE VH, Factor IX Concentrate (Human), is supplied in a single dose vial accompanied by a vial of Sterile Water for Injection, U.S.P. for diluent, a sterile transfer needle and a sterile filter needle as follows:

IMMUNINE VH (IU[1])	Sterile Water for Injection. USP (mL)
480 to 720	5

[1]The number of I. U. Factor IX is stated on the label of each vial.

6 DESCRIPTION

IMMUNINE VH, Factor IX Concentrate (Human), is a purified, sterile, freeze-dried concentrate of human blood coagulation factor IX. IMMUNINE VH is standardized in terms of factor IX content and each vial is labeled with the factor IX content indicated in international units (IU) (1, 2). One international unit of factor IX (based on the First International Standard for Factors II, IX and X in Coagulation Factor Concentrates Code 84/681) corresponds to the factor IX activity contained in 1 ml of fresh normal human plasma.

IMMUNINE VH is prepared from large pools of human plasma which may contain the causative agents of hepatitis and other viral diseases (see WARNINGS AND PRECAUTIONS).

7 WARNINGS AND PRECAUTIONS

General

IMMUNINE VH, Factor IX Concentrate (Human), should not be administered at a rate exceeding 2 mL/min.

IMMUNINE VH contains less than 0.1 IU heparin per ml. In case of surgical intervention in hemophilia B patients receiving replacement therapy with IMMUNINE VH, perioperative thrombosis prophylaxis with low-dose heparin is recommended in those situations where such a prophylaxis would normally be indicated in patients having no coagulation defect.

IMMUNINE VH contains not more than 5 µg TWEEN 80 per mL.

Driving and Operating Machinery
There is no information on the effects of IMMUNINE VH on the ability to operate an automobile or other heavy machinery.

Hematologic
Since the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the risk being higher in low purity preparations, the use of factor IX-containing products may be potentially hazardous in patients with disseminated intravascular coagulation (DIC) and in patients with signs of fibrinolysis.

Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing, in particular when administering this product to patients with liver disease, to patients peri- and postoperatively, or to other patients at risk for thrombotic events or DIC.

In patients with DIC or those at risk for DIC or thromboembolic events, the benefit of treatment with IMMUNINE VH should be weighed against the risk of these complications.

In patients with a risk of thrombosis (e.g. patients with a history of severe liver disease, thrombophilia, or a tentative or definite diagnosis of angina pectoris, coronary heart disease or myocardial infarction) the factor IX level should not be raised beyond 60% of normal. In addition, these patients - as well as patients receiving high doses of human blood coagulation factor IX concentrate for major surgery - should be monitored for the development of DIC and/or thrombosis.

Immune
Anaphylaxis/anaphylactoid and other severe hypersensitivity reactions have been reported with IMMUNINE VH. Patients and/or their caregivers should be informed of the early signs of hypersensitivity reactions. They should be advised to discontinue use of the product immediately and contact their physician if such symptoms occur. Minor reactions may be controlled by antihistamines, while the therapy of severe hypotensive reactions follows the current guideline of shock treatment.

As a plasma derived factor IX concentrate, the product contains other human proteins.

There have been reports in the literature showing an association between the occurrence of a factor IX inhibitor and allergic reactions, in particular in patients with a high-risk gene mutation. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor.

Because of the risk of allergic reactions with factor IX concentrates, the initial administrations of factor IX should be performed under medical observation where proper immediate medical care for severe allergic/anaphylactic reactions could be provided, in particular in patients with high risk gene mutations or where the mutation is unknown.

In case of shock, the current medical standards for shock treatment should be observed.

Monitoring and Laboratory Tests
During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of

coagulation analysis (plasma Factor IX activity) is indispensable. Individual patients may vary in their response to factor IX, achieving different levels of in vivo recovery and demonstrating different half-lives.

If bleeding does not resolve despite adequate treatment, clotting factor levels should be measured. Inhibitor testing should be performed if the level is unexpectedly low, as this may be an indication that factor IX inhibitor is present. Allergic reactions, including anaphylaxis is another indicator of inhibitor development and warrants inhibitor testing (see Warnings and Precautions).

Sensitivity/Resistance

Inhibitors

Patients with hemophilia B may develop neutralizing antibodies (inhibitors) to factor IX.

After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

If such inhibitors occur, the condition will manifest itself as an insufficient clinical response.

If a patient develops an inhibitor, it is recommended that a specialized hemophilia center be contacted.

Patients with factor IX inhibitors are at an increased risk of severe hypersensitivity reactions or anaphylaxis with subsequent challenges with factor IX.

Nephrotic syndrome has been reported following attempted immune tolerance induction in hemophilia B patients with factor IX inhibitors.

Sodium Content

The calculated sodium content of the IMMUNINE VH 600 IU formulation is 20.4 mg per vial. The quantity of sodium in a high single dose in adults may exceed 250 mg for the 600 IU/5mL formulation. This is to be taken into consideration in patients on a low-sodium diet.

This following example is based on the assumption of a 70 kg patient, needing a 99% increase, and using the formula 70 x 99 x 1.1 = 7623 Units needed.

In this example of 12.7 vials at 600 IU.

600 IU vials contain 20.4 mg sodium ≈ 259.08 mg Na+

Sexual Health
Fertility
The effects of IMMUNINE VH on fertility have not been established.

Viral Safety
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 agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) and for the non-enveloped virus hepatitis A 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., in hemolytic anemia).

Individuals who receive infusion of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly nonA, nonB hepatitis.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma derived factor IX concentrates.

7.1 Special Populations

7.1.1 Pregnant Women

There is no adequate data from the use of IMMUNINE VH in pregnant or lactating women.

Healthcare providers should balance the potential risks and only prescribe IMMUNINE VH if clearly needed.

7.1.2 Breast-feeding

The safety of IMMUNINE VH for use in lactating women has not been established. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing IMMUNINE VH.

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

7.1.3 Pediatrics

There is limited data available in children.

7.1.4 Geriatrics

There is no data available to determine whether subjects aged 65 and over respond differently from younger subjects.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

As with any infused plasma derivative, hypersensitivity reactions (e.g. fever, urticaria, nausea, vomiting, dyspnea, drop in blood pressure, shock) may occur rarely.

In rare cases, replacement therapy with human blood coagulation factor IX concentrates may lead to the formation of circulating antibodies which inhibit factor IX.

The possibility of thromboembolic complications cannot be entirely ruled out. This applies particularly to patients at risk for thrombosis and/or receiving high-dose therapy.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The adverse reactions presented in Table 1 have been identified from 5 prospective clinical trials (IMAG-036, IMAG-037, IMAG-092, IMAG-115, and IMAG-169) conducted with IMMUNINE VH (product with and without heparin) in 148 subjects administered 2807 infusions.

Study IMAG-036 was a prospective, controlled, randomized, cross-over study to investigate the pharmacokinetics and safety of IMMUNINE VH in patients with severe congenital FIX deficiency (< 0.01 IU/mL of FIX). All subjects were male. A total of 26 subjects (10 to 53 years of age) received IMMUNINE VH without heparin, 29 subjects (18 to 70 years of age) received IMMUNINE VH with heparin (containing approximately 0.05 IU heparin /IU FIX). Each subject received the study product (IMMUNINE VH) and the control product (BEBULIN3) in random order with an interval of at least 10 days between treatment phases.

Study IMAG-037 was a prospective, multi-center, open-label study to determine the efficacy, safety and lot consistency of IMMUNINE VH in hemophilia B patients with a FIX activity of < 0.25 IU/mL. All subjects (N=61) were male and between 0.6 and 70.2 years of age. They could receive IMMUNINE VH for acute hemorrhages, for emergency treatment, and/or for surgical prophylaxis.

Study IMAG-092 was a prospective, open-label, non-controlled, multi-center, international study to monitor the safety of Baxter's PCR screened blood products in non-infected patients. Of 18 subjects who completed the study, 10 received IMMUNINE VH. All subjects were male, their age ranged between 2 and 66 years.

Study IMAG-115, a prospective, open-label, phase IV study in patients previously untreated with IMMUNINE VH with severe congenital FIX deficiency (< 0.01 IU/mL), was conducted to determine the pharmacokinetics, efficacy and safety of IMMUNINE VH. All subjects (N=7) were male and between 5 and 50 years of age.

Study IMAG-169 was a phase III/IV, prospective, open-label, un-controlled, multi-center, international study in previously treated patients with hemophilia A or B to monitor for FVIII and FIX inhibitor development and viral safety. Of 43 subjects, 15 received IMMUNINE VH. All subjects were male and were between 17 and 44 years of age.

Table 1: Adverse Reactions from Clinical Trials

System Organ Class (SOC)	Adverse Reaction	Frequency	
		Category	Frequency Ratio (Percentage)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Throat irritation	Uncommon	3/2807 (0.11%)
	Oropharyngeal pain	Rare	1/2807 (0.04%)
	Cough (dry)	Rare	1/2807 (0.04%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash	Uncommon	1/2807 (0.04%)
	Pruritus	Rare	1/2807 (0.04%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia	Rare	1/2807 (0.04%)

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

Inhibitor development to factor IX has been reported (see Section on Post-Market Adverse Drug Reactions). In clinical trials with IMMUNINE VH, no factor IX inhibitors were identified in 41 patients having a total of 2079 exposure days to IMMUNINE VH in the clinical trials. No previously untreated patients were enrolled in IMMUNINE VH clinical trials.

8.3 Less Common Clinical Trial Adverse Reactions

Please refer to the Adverse Reactions from Clinical Trials Table above.

8.4 Post-Market Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA (vers.15.0) System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

Blood and Lymphatic System Disorders: Factor IX Inhibition

Immune System Disorders: Anaphylactic/Anaphylactoid Reaction, Serum Sickness (In The Presence Of Inhibitors), Hypersensitivity Reaction

Nervous System Disorders: Headache

Cardiac Disorders: Myocardial Infarction, Tachycardia

Vascular Disorders: Flushing

Respiratory, Thoracic, And Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Urticaria

General Disorders and Administration Site Conditions: Chills

Class Reactions

Disseminated intravascular coagulation, thromboembolic episodes (e.g., pulmonary embolism, venous thrombosis, arterial thrombosis, cerebral artery thrombosis)

Other manifestations of hypersensitivity or allergic reactions: anaphylactic shock, angioedema, chest tightness, hypotension, lethargy, nausea, vomiting, paresthesia, restlessness, wheezing.

Nephrotic syndrome (following attempted immune tolerance induction)

9 DRUG INTERACTIONS

9.1 Overview

No interactions of human coagulation factor IX products with other medicinal products are known.

As for any blood coagulation factor concentrate IMMUNINE VH Factor IX Concentrate (Human) should not be mixed with other drugs. It is advisable to rinse a common venous access with isotonic saline prior to and after infusion of IMMUNINE VH.

9.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Coagulation factor IX is one of the clotting factors found in normal human blood and is required for normal clot formation. Intravenous administration of IMMUNINE VH, Factor IX Concentrate (Human) provides an increase in plasma levels of factor IX and can temporarily correct the coagulation defect of patients with factor IX deficiency.

The in vivo recovery and half-life of IMMUNINE VH were evaluated in 26 patients with severe hemophilia B (factor IX levels below 1 %) and no bleeding at the time of testing. The patients received a single infusion of 50-70 units IMMUNINE VH per kg body weight. The mean increase in the patients' factor IX plasma levels was 0.92 percent per administered IU factor IX per kg body weight, corresponding to a recovery of 41%. The average biological half-life was approximately 17 hours. These data are based on calculations using the new International Standard for Human Blood Coagulation Factors II, IX and X in Concentrates Code 84/681.

10.2 Pharmacodynamics

Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin-K dependent coagulation factor and it is synthesised in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed. Hemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

10.3 Pharmacokinetics

In vivo recovery and half life characteristics were evaluated in an international, prospective, controlled, cross-over study following ISTH guidelines. A total of 26 patients with an age of more than 12 years with severe hemophilia B (factor IX level < 1 %), and not bleeding at the time of testing, have been given a single infusion of 50-70 IU/kg body weight at 10 day intervals of either IMMUNINE VH or BEBULIN VH, IMMUNO's Factor IX Complex licensed in Canada since 1988. Mean half life observed was 17.42 h for IMMUNINE VH vs. 18.77 h for BEBULIN VH whereas mean in vivo recovery was 0.92 percent per administered IU factor IX per kg bodyweight for IMMUNINE VH vs.1.02 percent for BEBULIN VH.

11 STORAGE, STABILITY AND DISPOSAL

When stored between +2°C and +8°C (+35°F and +46°F), IMMUNINE VH, Factor IX Concentrate (Human) is stable until the date indicated on the label.

Within the indicated shelf life IMMUNINE VH may temporarily be stored at room temperature [up to +25°C (+77°F)] for a period of up to 3 months. Record the period of storage at room temperature below the expiration date indicated on the package label. Discard product if stored at room temperature for three months.

IMMUNINE VH must not be used beyond the expiration date indicated on each pack.

Reconstituted Solutions

The reconstituted solution should be used immediately after preparation (contains no preservative), it should not be refrigerated and any unused portion of it should be discarded (See DOSAGE AND ADMINISTRATION).

12 SPECIAL HANDLING INSTRUCTIONS

IMMUNINE VH is to be reconstituted only immediately before administration. The solution should then be used promptly (preparation does not contain any preservatives).

The product should be inspected visually prior to reconstitution and administration. The lyophilised powder or friable solid should be white or pale yellow. The solution should be clear or slightly opalescent. Do not administer if particulate matter or discoloration or cloudiness is found upon reconstitution; contact Takeda Customer Service.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Factor IX Concentrate (Human)

Chemical name: Not applicable

Molecular formula and molecular mass:

Human blood coagulation factor IX (Factor IX), is a single chain glycoprotein consisting of 415 amino acids with relative molecular mass of 57,000 Da.

Structural formula:

Factor IX contains 12-gamma-carboxylated glutamic acid residues, two epidermal growth factor regions, one activation peptide domain, and a serine protease region.

Physicochemical properties:

Factor IX is the zymogen from the serine protease Factor IXa. After activation and removal of the activation peptide, Factor IXa is a disulfide-linked two-chain serine protease specific for an arginine–isoleucine bond. Factor IXa and Factor VIIIa form a high-affinity complex on the phospholipid surface in the presence of calcium to activate Factor X by cleaving a single peptide bond in the aminoterminal region of the heavy chain.

Product Characteristics

IMMUNINE VH is a highly purified factor IX concentrate containing only traces of other coagulation factors (up to 0.02 IU of factors II, VII and X per IU factor IX). In preclinical trials utilizing supra-therapeutic doses of IMMUNINE VH no thrombotic adverse reactions were observed. IMMUNINE VH is prepared from pooled human plasma.

IMMUNINE VH contains less than 0.1 IU heparin per ml and not more than 5µg TWEEN 80 per ml.

The manufacturing process includes key stages, among them a product-specific vapor heat treatment, that have been shown to result in removal and inactivation of infectious agents.

Individual donations of human plasma are combined to form plasma pools. Prior to being used for manufacture of IMMUNINE VH, each plasma pool is tested for the presence of genome sequences of the human immunodeficiency virus type 1, hepatitis B virus (HBV), and hepatitis C virus (HCV) using IQ-PCR[2].

[2] IQ-PCR: IMMUNO Quality Assured Polymerase Chain Reaction
With this method 500 genome equivalents/ml of the above viruses can be determined reliably, with the actual sensitivity of IQ-PCR being below that. Therefore all pools which have been tested and evaluated as being sensitivity lead to exclusion from further processing. No correlation has been demonstrated between infectivity and removal of pools containing these levels of genomic equivalents from further manufacturing.

To prevent the transmission of infective agents by the administration of IMMUNINE VH, prescribed procedures are used for the collection and testing of the source plasma and during the manufacture of the product. They include measures taken for donor and plasma selection[3], as well as virus removal and inactivation steps during manufacturing.

Viral Inactivation
A virus panel representing a wide range of physicochemical characteristics was used in virus clearance studies investigating the virus reduction capacity of the IMMUNINE VH production process. Whenever feasible relevant target viruses, i.e. viruses, which could potentially be present in human plasma, were used in the virus clearance studies:

Human Immunodeficiency virus type I (HIV-1) and Hepatitis A Virus (HAV) were used as target viruses.

For viruses which cannot be titrated in established cell lines, e.g. HCV and Parvovirus B19, model viruses were used:

Pseudorabies virus (PRV, an enveloped DNA virus as a generic model for hepatitis B virus), Bovine Viral Diarrhea Virus (BVDV, a small enveloped RNA virus as a model for HCV) and Mice Minute Virus (MMV, small, non-enveloped DNA virus as model virus for Parvovirus B19 and other small, non-enveloped DNA viruses).

A summary table of the virus validation studies performed is given below. Intermediates of IMMUNINE VH were obtained from the manufacturing facility. Aliquots of the intermediate were spiked with viruses and the virus inactivation/removal capacity of the respective process step was investigated. Mean reduction factors are listed in the table below. Where two or more reduction factors are available for a specific manufacturing step, the mean value was used to calculate the ORF.

Virus Validation Studies- Summary Table

	Log_{10} Reduction Factor					
Intermediate (Step)	**HIV-1**	**HAV**	**PRV**	**BVDV**	**MMV[4]**	**B19V**
Purification of Factor IX complex from cryosupernatant with DEAE-Sephadex	n.d.	1.4	n.d.	n.d.	1.3	3.6 (PCR)

[3] All plasma units used for manufacture are ALT tested and non-reactive in tests for HBs-antigen and antibodies to HCV, HIV-1 and HIV-2. Before further processing all individual plasma donations are subjected to an inventory hold of at least three months for a possible look- back of plasma donations suspected of infection.
[4] MMV is however, not an appropriate B19V model for heat treatment steps as MMV is substantially more heat resistant than B19V, as also evident by the two publications cited below:
- M.Yunoki et al., Heat sensitivity of human parvovirus B19, Vox Sanguinis (2003) 84, 164-169
- Blümel et.al., Inactivation of parvovirus B19 during pasteurization of human albumin, Transfusion (2002),42, 1011- 1018

Polysorbate 80 treatment followed by Ion Exchange Chromatography[5]	>5.1	2.8	3.4	>4.7	1.2	n.d.
Freeze Drying & Vapor Treatment	>6.6	>4.2	>7.6	>6.6	1.3	n.d.
Overall Log_{10} Reduction Factor (ORF)	**>11.7**	**>8.4**	**>11.0**	**>11.3**	**3.8**	**3.6**

n.d. not determined

In prospective clinical studies as well as in post-marketing surveys, the risk of transfusion-transmitted viral infections was followed up in patients given factor concentrates of the prothrombin complex subjected to the same vapor heat treatment as IMMUNINE VH. Using the criteria established by the ISTH, 45 patients were evaluated for non-A/non-B transmission and 27 for hepatitis B transmission. In addition, 42 patients were evaluated for HCV seroconversion, and 105 for HIV seroconversion. No cases of product related viral hepatitis or HIV transmission were observed.

[5] For HIV-1 and BVDV, the reduction factors apply to the P80 treatment only.

14 NON-CLINICAL TOXICOLOGY

In the test for acute toxicity following intravenous application in mice and rats it was shown that the maximum dose which did not cause death of the animals was 21 (mice) and 16.7 times (rats) higher than the maximum dose recommended in humans.

Studies on subacute and chronic toxicity as well as studies on reproduction toxicity and mutagenic or tumorigenic potential were not performed since repeated administration of Factor IX would be liable to cause the formation of antibodies in the animals. Results obtained in the animal model would hence not allow extrapolation to humans.

When tested in rabbits using the Wessler method of assessing thrombogenicity IMMUNINE VH failed to show any evidence of thrombogenicity even at a dose of 1000 IU/kg.

When IMMUNINE VH was administered intra-arterially to guinea pigs at a dose of 200 IU/kg no anaphylactoid effects were noted.

Following administration of IMMUNINE VH in an anesthetized dog model (200 1U/kg i.v.) no changes in blood pressure, heart rate or ECG were observed.

Data on the efficacy of the vapor heat treatment on viral safety of the preparation have been previously described in the section ACTION AND CLINICAL PHARMACOLOGY.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

IMMUNINE® VH
Factor IX Concentrate (Human)

Read this carefully before you start taking **IMMUNINE VH** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IMMUNINE VH**.

What is IMMUNINE VH used for?
- IMMUNINE VH is a Factor IX protein used for therapeutic and prophylactic (preventative) use in patients suffering from congenital (haemophilia B) or acquired factor IX deficiency.

How does IMMUNINE VH work?
IMMUNINE VH is administered by intravenous (IV) therapy and provides an increase in plasma levels of factor IX. IMMUNINE VH can temporarily correct the coagulation defect of patients with factor IX deficiency and therefore stop the bleeding episodes.

What are the ingredients in IMMUNINE VH?
Medicinal ingredients: Freeze dried Factor IX concentrate of high purity containing traces of Factors II, VII and X (<0.02 IU / 1 IU factor IX)
Non-medicinal ingredients: Factor II, VII and X (<0.02 IU / 1 IU factor IX), Sodium Chloride, Sodium Citrate and Sterile Water for Injection, Tween 80

IMMUNINE VH comes in the following dosage forms:
IMMUNINE VH is a sterile freeze-dried powder and supplied in a single dose vial accompanied by a vial of Sterile Water for Injection, EP as diluent, a sterile transfer needle, and a sterile filter needle. It is available in the following package sizes:

IMMUNINE VH (IU)	Sterile Water for Injection EP (mL)
480 to 720	5

The number of IU Factor IX is stated on the label of each vial.

Do not use IMMUNINE VH if:
- You suffer from DIC and/or hyperfibrinolysis; or
- You have a known allergy to heparin or history of heparin induced thrombocytopenia; or
- You experience hypersensitive reactions occurs during administration of IMMUNINE VH; or
- You are pregnant or nursing mothers (only use if clearly needed); or
- You have had a recent myocardial infarction, stroke or thromboembolic events

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IMMUNINE VH. Talk about any health conditions or problems you may have, including if you:
- You have known allergies to this drug, to heparin, or to any ingredient in the formulation or

component of the product
- You have thromboembolism, DIC, or fibrinolysis
- You are pregnant or may be pregnant
- You are a nursing mother

Other warnings you should know about:
Because IMMUNINE VH is made from human plasma, a risk of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The use of IMMUNINE VH may lead to hypersensitivity reactions. Hypersensitivity reactions refer to undesirable reactions produced by the normal immune system such as allergies. At first signs or symptoms of hypersensitivity reactions, IMMUNINE VH treatment should be stopped and medical care should be started as appropriate.

Your body may form inhibitors to factor IX. An inhibitor is an antibody (part of your body's normal immune defenses) that forms in response to infusions of factor IX that prevents the factor IX from working properly. These inhibitors can lead to a reduced response or to no response to factor IX therapy. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors.

The use of factor IX may lead to the development of blood clots in your veins. This is particularly dangerous if you have disseminated intravascular coagulation (DIC) or fibrinolysis. If you have DIC or are at risk of DIC, please discuss with your doctor whether the use of IMMUNINE VH is right for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with IMMUNINE VH:
- No interactions with other drugs are currently known. IMMUNINE VH should not be mixed with other drugs

How to take IMMUNINE VH:
See Usual dose.

Usual dose:
The dose of the treatment depends on the severity of factor IX deficiency, the location and extent of the bleeding, and the patient's clinical condition. The treatment should be carried out by a doctor who is familiar with the treatment of haemophilia.

Overdose:
Overdosage may increase your risk of myocardial infarction, DIC, venous thrombosis, and pulmonary embolism.
IMMUNINE VH, should not be administered at a rate exceeding 2 mL/min.

If you think you have taken too much IMMUNINE VH, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Not applicable

What are possible side effects from using IMMUNINE VH?

These are not all the possible side effects you may feel when taking IMMUNINE VH. If you experience any side effects not listed here, contact your healthcare professional.

- Although rare, severe allergic reactions may occur.
- If you develop fever, skin rashes, nausea, retching, shortness of breath, a drop in blood pressure or shock you should stop the use of IMMUNINE VH and contact your doctor or visit the Emergency Department immediately.
- Mild allergic reactions may be managed with antihistamine.

The following side effects have been reported:
- Allergic reaction
- Headache
- Myocardial Infarction, Tachycardia
- Flushing
- Shortness of Breath
- Skin rashes
- Chills

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
IMMUNINE VH should be stored in the refrigerator at a temperature between 2°C and 8°C.

IMMUNINE VH may be temporarily stored at room temperature (up to +25°C) for a period of up to 3 months. Record the period of storage at room temperature below the expiration date indicated on the package label. Dispose of the product if stored at room temperature for three months or longer.

IMMUNINE VH must not be used beyond the expiration date indicated on each pack.

The reconstituted solution contains no preservatives and should be used immediately after

preparation. Dispose of any unused portion. Do not refrigerate any unused portion.

Keep out of reach and sight of children.

If you want more information about IMMUNINE VH:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.takeda.com/en-ca, or by calling 1-800-268-2772.

This leaflet was prepared by

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