PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

Haemosolvex Factor IX®, 500 IU/10 ml, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Factor IX Complex

When each vial of the product is reconstituted with the 10 ml Water for Injection provided, the solution per vial will contain factor IX 500 IU (50 IU/ml), factor II > 400 IU, factor VII > 65 IU and factor X > 400 IU.

Factor IX complex (prothrombin complex) is a lyophilised concentrate containing the following coagulation factors: factor II (prothrombin), factor VII (proconvertin), factor IX (Christmas factor) and factor X (Stuart-Prower factor).

Haemosolvex Factor IX is prepared from pooled fresh plasma donated by healthy, non-remunerated donors. Each unit of plasma has been individually tested and found non-reactive for hepatitis B surface antigen, antibodies to the hepatitis C virus and antibodies to the human immunodeficiency viruses, HIV-1 and HIV-2, using approved methods.

To reduce the risk of transmission of infective agents, selection of donors and donations by suitable measures is performed and removal and/or inactivation procedures are included in the production process. The manufacturing method includes a process of solvent detergent treatment developed to inactivate lipid-enveloped viruses. The efficacy of this process has been tested against hepatitis B, hepatitis C and HIV.

The preparation has been tested and found negative for the presence of active thrombin. The product is stabilised with 10 IU heparin per ml. The reconstituted solution is isotonic with a sodium content of approximately 300 mmol/L.

Contains sugar (sucrose): not more than 1,1 g per 10 ml vial

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

Lyophilised powder: A friable, off-white to light blue powder.

Haemosolvex Factor IX has a pH of between 4,0 and 7,4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Haemosolvex Factor IX may be used for the treatment of coagulation defects caused by either a congenital or an acquired deficiency of factor IX.

Congenital: Haemophilia B.

Acquired: The treatment of severe bleeding resulting from an overdose of oral coumarin-derivative anticoagulants.

4.2 Posology and method of administration

Warnings:

Measures to treat anaphylaxis, including adrenaline and corticosteroids, must be at hand when administering **Haemosolvex Factor IX**.

If a gel forms on reconstitution, the preparation must not be used.

Do not administer concomitantly with other medicines (see section 4.5).

Posology

Individualised dosage:

The dosage and duration of treatment is based on the patient's body mass, type of haemorrhage, location of the bleed, type of surgery to be performed and the clinical picture.

Paediatric population

Paediatric factor IX dose: Dose is calculated according to the body mass. Refer to the determination of dosage section.

The determination of the factor IX plasma level is useful initially in determining the dose required and thereafter in assuring whether adequate factor IX concentrations have been achieved and are being maintained.

Determination of the dosage:

The calculated required dosage for treatment is based on the empirical finding that 1 IU of factor IX per kg body weight raises the plasma factor IX activity by 0,8 % of normal.

The required dosage is determined using the following formula (initial dose):

Required units (IU) = Body weight (kg) x desired factor IX increase (%) x 1,2

The amount to be administered and the frequency of administration should always be oriented towards clinical efficacy and therefore the recommended dosage regimens must be used as a guideline for therapy only. Longer or shorter periods and higher or lower levels of replacement therapy may be necessary.

Treatment guidelines:

Haemorrhagic event (with examples)	**Therapeutically necessary plasma level of factor IX activity**	**Period during which it is necessary to maintain the therapeutic plasma level of factor IX activity**
Minor: Spontaneous early bleed; Minor oral bleeds; Nasal haemorrhage; Trauma without the signs of bleeding; Haematuria without pain.	30 %	At least one day, depending on the severity of the haemorrhage.
Major: Oral bleeds (including molar tooth extraction and haemorrhage of the throat and tongue); Full symptoms of haemarthrosis; Haemorrhage in the calf or the forearm; Mild trauma capitis; Severe epistaxis; Retroperitoneal bleeding; Trauma with bleeding; Haematuria with pain. Serious injuries; Major operations; Intracranial haemorrhage; Gastro-intestinal haemorrhage.	30 - 50 % 50 - 75 %	3 - 4 days or until adequate wound healing (see “5.2 Pharmacokinetic properties”)
Anticoagulant	30 %	At least one day, depending on

haemorrhage		the severity of the haemorrhage.

Prevention of bleeding during and following surgical procedures:
Replacement therapy must be initiated one hour prior to the procedure. The factor IX level must be maintained high enough to prevent haemorrhage and promote epithelialisation until healing is complete and sutures are removed (see 'Treatment guidelines'). Concurrent antifibrinolytic therapy to prevent or decrease bleeding during and following dental surgery may be required (see section 4.4).

Method of administration

For instructions on dilution of the medicinal product before administration, see section 6.6.
This preparation must be administered as a slow intravenous infusion over at least 2 minutes.

4.3 Contraindications

Hypersensitivity to the active substance (human factor IX complex) or to any of the excipients listed in section 6.1.

This product should not be administered to patients with a high risk of thrombosis or disseminated intravascular coagulation (DIC).
This preparation is not intended for the treatment of haemophilia A (classical haemophilia) due to factor VIII deficiency.
Do not use the factor IX complex, unless the deficiency has been confirmed.
Factor IX complex is ineffective in bleeding due to heparin.
Factor IX complex should not be given in cases of liver damage, with evident

antithrombin III deficiency as coagulation activation with paradoxical haemorrhage occurs.

4.4 Special warnings and precautions for use

Transmissible agents

Infectious diseases due to the transmission of infectious agents cannot be totally excluded. Consideration should be given to appropriate vaccination of patients receiving human blood or plasma-derived medicinal products.

Dental

Caution should be exercised when administering systemic antifibrinolytics in conjunction with factor IX complex as they may potentiate the thrombogenic effects of factor IX complex concentrates. Using the antifibrinolytic agent as an oral rinse, or delaying its use for 8 to 12 hours after administration of the concentrate, may minimise this complication.

Thromboembolism

Because of the potential risk of thrombo-embolic complications, caution should be exercised when administering **Haemosolvex Factor IX** to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thrombo-embolic episodes.

The potential benefit of treatment with high doses (> 50 %) of factor IX complex concentrate should be weighed against the risk of complications resulting from withholding administration.

Patients receiving high doses for 4-5 days of treatment should be carefully monitored for potential complications.

Inhibitors

If the patient is not responsive to therapy, consideration should be given to the presence of inhibitors (antibodies to factor IX).

Prevention of bleeding during and following surgical procedures (see section 4.2).

This medicine contains 69 mg sodium per 10 ml vial equivalent to 3,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Do not administer concomitantly with other medicines (see section 4.2).

4.6 Fertility, pregnancy and lactation

No data is available on fertility, pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Haemosolvex Factor IX has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Allergic/anaphylactic type reactions, characterised by chills, fever and urticaria, may occur.

In the event of acute anaphylactic shock, the injection must be stopped immediately and appropriate treatment initiated.

Other adverse events such as nausea, vomiting, headache and flushing have been reported, particularly following rapid administration. Factor IX

complex concentrates have been associated with thrombo-embolic complications, with reports of thrombosis and intravascular coagulation in patients with liver disease. Myocardial infarction has occurred in patients receiving factor IX complex concentrates, and may be associated with high doses.

Tabulated list of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Unknown	Disseminated intravascular coagulation
Immune system disorders	Unknown	Anaphylactoid reaction Hypersensitivity
Nervous system disorders	Unknown	Headache
Cardiac disorders	Unknown	Myocardial infarction
Vascular disorders	Unknown	Flushing Thrombosis
Gastrointestinal disorders	Unknown Unknown	Nausea Vomiting

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and

eReporting platform (https://primaryreporting.who-umc.org/ZA) found on SAHPRA website or to National Bioproducts Institute NPC via the email address Pharmacovigilance@nbisa.org.za.

4.9 Overdose

The use of high doses or prolonged continuous usage of factor IX complex concentrates, has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism, due to accumulation of factors II and X. Therefore, in cases of overdosage, the development of thrombo-embolic complications or disseminated intravascular coagulation is enhanced in patients at risk of these complications.

Appropriate measures for the treatment of thrombo-embolic complications or disseminated intravascular coagulation should be initiated, should these occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, Blood coagulation factors IX, II, VII and X in combination, ATC code: B02BD01.

Category and class: A 30.3 Biologicals (Blood Fractions)

Factor IX is a vitamin K-dependant clotting factor synthesised in the liver.

Factor IX is part of the intrinsic pathway of blood coagulation and is required for the pathway’s completion. This pathway results ultimately in the conversion of prothrombin to thrombin and thereby facilitates the formation of a fibrin clot.

Haemosolvex Factor IX complex also contains vitamin K-dependant coagulation factors II, VII and X.

In anti-coagulant haemorrhage (e.g. coumarin medicine overdose), the coumarin-derivative anticoagulants act indirectly in the liver by inhibiting the vitamin K-mediated gamma-carboxylation of precursor proteins, thus preventing the usage of these factors in the clotting cascade. The administration of factor IX complex concentrates containing additional vitamin K-dependant clotting factors, increases the plasma concentration of these clotting factors to overcome the effect of the anticoagulant.

5.2 Pharmacokinetic properties

The plasma half-life of factor IX ranges from 16-30 hours. The plasma half-life of factor II ranges from 40-60 hours, factor VII from 3-6 hours, and factor X from 30-60 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Heparin sodium injection

Hydrochloric acid (for pH-adjustment)

Sodium chloride

Sodium hydroxide (for pH-adjustment)

Sucrose

Tri-sodium citrate dihydrate

Water for injections

6.2 Incompatibilities

In the absence of incompatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

3 years.

Administer the solution as soon as possible after reconstitution but not more than three hours after reconstitution. See section 6.6.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep vial in the outer carton until required for use.

For in-use storage conditions, see section 6.3

6.5 Nature and contents of container

500 IU: Haemosolvex Factor IX powder for solution for infusion is packed in a clear Type I glass, evacuated, 30 ml vial sealed with a chlorobutyl rubberclosure and an aluminium seal with a black flip-off cap.

Each pack consists of one vial of **Haemosolvex Factor IX**, 10 ml water for injections clear glass ampoule, a reconstitution set and an administration set.

6.6 Special precautions for disposal and other handling

RECONSTITUTION PROCEDURE

Read all instructions before commencing the reconstitution procedure.

Use only the injection/infusion set supplied as Haemosolvex Factor IX must be administered via plastic syringes only and filtered before use.

1. Remove the plastic cap from the stopper of the product vial and swab the exposed rubber stopper with a suitable anti-bacterial agent.
2. Attach the FILTER NEEDLE (short metal needle) to the syringe. This must remain attached until just before infusion.

3. Open the diluent and draw up 10 ml of Water for Injection. See figure 1.

   Insert the filter needle, with syringe attached, through the stopper of the product vial.



Figure 1

4. The vacuum will draw the diluent into the vial. See figure 2.

   Rotate the vial to ensure complete wetting of the powder.



Figure 2

5. Gently swirl the vial until the powder is dissolved. Do not shake and avoid foaming. The reconstitution process should take 30 minutes at the most.

   The reconstituted solution is colourless to light blue.

   Do not use if the solution is turbid or contains particulate matter or if a gel forms after reconstitution.

6. When the solution is ready for administration, after complete dissolution, pierce the stopper with the AIR VENT needle to release the remaining vacuum in the vial. Remove and discard the air vent needle.

7. Withdraw the contents of the vial into the syringe. See figure 3.



Figure 3

8. Remove the syringe and the filter needle from the vial. Invert the syringe, expel any air, then remove and discard the filter needle.
9. Attach the BUTTERFLY NEEDLE to the syringe. See figure 4.



Figure 4

10. Administer the solution as soon as possible after reconstitution but not more than three hours after reconstitution, as a slow intravenous infusion over at least 2 minutes
11. Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

NATIONAL BIOPRODUCTS INSTITUTE NPC

Reg. No. 1994/002044/08

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8 REGISTRATION NUMBERS

W/30.3/191

NAMIBIA	S2
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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 January 1991

10 DATE OF REVISION OF THE TEXT