MODULE 1.3 SOUTH AFRICAN LABELLING AND PACKAGING

1.3.1 South African Package Insert
1.3.1.1 Proposed Package Insert

SCHEDULING STATUS **S4**

PROPRIETARY NAME (AND DOSAGE FORM)

Haemosolvate ® Factor VIII 300 IU (Powder for Injection)

Haemosolvate ® Factor VIII 500 IU (Powder for Injection)

COMPOSITION

Descriptive name: Human factor VIII concentrate

This lyophilised concentrate, with a high specific factor VIII (factor VIII: C) and von Willebrand factor (factor VIII: vWF) activity, is prepared from pooled fresh human plasma sourced from healthy blood 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.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human plasma include the 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 plasma are administered, the possibility of infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken during the manufacture of **Haemosolvate Factor VIII** (solvent/detergent - treatment) are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19 (See "**WARNINGS AND SPECIAL PRECAUTIONS**").

300 IU: When each vial of the product is reconstituted with the 10 ml Water for Injection, the solution (per vial) will contain factor VIII:C – 300 IU; factor VIII:vWF - > 300 IU;
Inactive ingredients: sucrose – ≤ 0,31 g; protein - not more than 0,15 g, of which not more than 80 % is fibrinogen.

500 IU: When each vial of the product is reconstituted with the 10 ml Water for Injection, the solution (per vial) will contain factor VIII:C – 500 IU; factor VIII:vWF - >500 IU;
Inactive ingredients: sucrose – ≤ 0,31 g; protein - not more than 0,25 g, of which not more than 80 % is fibrinogen.

PHARMACOLOGICAL CLASSIFICATION

A 30.3 Biologicals (Blood Fractions)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Factor VIII is an endogenous glycoprotein necessary for blood clotting and haemostasis. It is a cofactor necessary for factor IX to activate factor X in the intrinsic pathway. In haemophilia A, there is a deficiency of this clotting factor. The average normal plasma activity of factor VIII is designated 100 % and a factor VIII concentration of 25 % of normal is required for haemostasis. Patients with severe haemophilia have a factor VIII concentration of less than 1 % of normal, and frequently experience bleeding even in the absence of trauma. Patients with factor VIII concentrations between 1 and 5 % (moderate haemophilia) experience less bleeding, and patients with a factor VIII concentration greater than 5 % (mild haemophilia) usually experience bleeding only after obvious trauma. The administration of **Haemosolvate Factor VIII** temporarily replaces the missing clotting factor to stop or prevent bleeding episodes.

Von Willebrand disease is characterised by abnormalities of von Willebrand factor (vWF), a large multimeric molecule which is bound to factor VIII. Von Willebrand factor is necessary for platelet adhesion to subendothelial tissue. Due to low level of the carrier protein, vWF, factor VIII levels are also diminished. The administration of **Haemosolvate Factor VIII** temporarily replaces the missing vWF to stop or prevent bleeding episodes.

Pharmacokinetic properties:

Factor VIII is immediately and completely bioavailable in the recipients' circulation after intravenous administration. Time to peak effect is 1 to 2 hours after intravenous administration. The half-life of factor VIII varies between 8 and 20 hours, with an average of 12 hours.

INDICATIONS

Treatment and prophylaxis of coagulation defects caused by congenital or acquired factor VIII deficiency:

Haemophilia A;

Acquired or congenital factor VIII deficiency with low levels of factor VIII inhibitor (refer to 'Patient monitoring - Detection and quantification of inhibitors');

Von Willebrand disease with factor VIII deficiency.

CONTRA-INDICATIONS

Haemosolvate Factor VIII should not be used to replace any other factor deficiency, factor IX, factor XI, etc., other than factor VIII deficiency.

Do not use unless a factor VIII deficiency has been verified.

Severe allergic reaction to **Haemosolvate Factor VIII**

WARNINGS AND SPECIAL PRECAUTIONS

This preparation must be administered by slow intravenous infusion.

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

If a gel forms on reconstitution, the preparation must not be used. Do not give concomitantly with other medicines.

Patients treated with **Haemosolvate Factor VIII**, should be carefully monitored for the development of inhibitors (antibodies to factor VIII). (See 'Patient monitoring'.)

Parvovirus B19 infection may be serious for pregnant women (foetal infection) (see "**PREGNANCY AND LACTATION")** and for individuals with immunodeficiency or increased red cell production (e.g. haemolytic anaemia).

Special precautions:

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

It is strongly recommended that every time that **Haemosolvate Factor VIII** 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.

Prevention of bleeding during and following surgical procedures (see "**DOSAGE AND DIRECTIONS FOR USE"**)

INTERACTIONS

No specific interactions of **Haemosolvate Factor VIII** products with other medicinal products are known.

PREGNANCY AND LACTATION

The safety of human plasma coagulation factor VIII concentrate in pregnancy has not been established in controlled clinical trials. Therefore **Haemosolvate Factor VIII** should only be

considered for use in well-informed pregnant patients after careful risk-benefit analysis. (see "**WARNINGS AND SPECIAL PRECAUTIONS"**)

DOSAGE AND DIRECTIONS FOR USE

General dosing information:

Dissolve each vial of the preparation before use by adding 10 ml Water for Injection (see reconstitution procedure).

Individualised dosage:

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

Patient monitoring:

The following may be useful in patient monitoring to determine the dosage required:

Plasma factor VIII determination:

To ensure that adequate factor VIII concentrations have been achieved and are maintained.

Detection and quantification of inhibitors:

This predicts whether or not the patient will respond to treatment. Patients with low inhibitor concentrations (< 5 Bethesda Units) may be managed by using increased doses of factor VIII to complex with and thereby inactivate the antibodies. However, patients with high inhibitor concentrations (> 5 Bethesda Units) are not likely to respond, and specific therapy is necessary. Patients with low inhibitor concentrations with an anamnestic response should be treated as a patient with a high inhibitor concentration.

Determination of the dosage:

One international unit of factor VIII activity is equivalent to that quantity of factor VIII in 1 ml of normal

human plasma. The calculation of the required dosage of factor VIII is based on the finding that administration of one IU of factor VIII per kg body mass, results in a ± 2 % increase in the factor VIII plasma concentration. The following formula may be used as a guide to calculate the required dose:

Required Units =

body mass (kg) x 0,5 x desired factor VIII increase (% of normal).

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

PROPHYLAXIS OF HAEMORRHAGE:

The aim is to keep factor VIII trough levels above 1 %. Dosages and dosage intervals range from 20 to 40 IU/kg intravenously every two to three days.

TREATMENT OF HAEMORRHAGE:

The amount to be administered and the frequency of administration should always be oriented towards clinical efficacy and therefore the recommended dosage regimes must be used as a guideline for therapy only.

Haemorrhagic event	**Therapeutically necessary plasma level of factor VIII activity**	**Frequency of dose (Refer to Pharmaco-kinetic properties)**	**Duration of therapy**

Mild haemorrhage Early haemorrhage into muscles/joints Early haemorrhages in the oral cavity	20 – 40 %	Repeat every 12 - 24 hours.	At least 1 day, until the bleeding episode as indicated by pain, is resolved or healing is achieved.
Moderate haemorrhage Haemorrhage into muscles/joints Haemorrhages in the oral cavity Haematoma	30 – 60 %	Repeat infusion every 12 - 24 hours.	3 – 4 days or until pain and acute disability are resolved.
Severe, life/limb-threatening haemorrhage Gastro-intestinal bleeding Intracranial, intra-abdominal or intra-thoracic haemorrhages Fractures	60 – 100 %	Repeat infusion every 8 - 24 hours.	Until threat is resolved.

PREVENTION OF BLEEDING DURING AND FOLLOWING SURGICAL PROCEDURES:

Replacement therapy must be initiated one hour prior to the procedure. The factor VIII level must be maintained high enough to prevent haemorrhage and promote epithelialisation until healing is complete and sutures are removed. Concurrent antifibrinolytic therapy to prevent or decrease bleeding during and following surgery may be required. (see "**WARNINGS AND SPECIAL PRECAUTIONS**")

Haemorrhagic event	**Therapeutically necessary plasma level of Factor VIII activity**	**Frequency of dose** **(Refer to Pharmaco-kinetic properties)**	**Duration of dose**
Tooth extraction (concurrent antifibrinolytic therapy) Minor operations	30 – 60 %	Every 24 hours	At least 1 day, until healing is achieved.
Major operations	80 – 100 %	Repeat infusion every 8 - 24 hours.	Until adequate wound healing, then therapy for at least another 7 days to maintain factor VIII activity of 30 - 60%.

In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

VON WILLEBRAND DISEASE: TREATMENT OF BLEEDING COMPLICATIONS AND SURGICAL INTERVENTIONS:

The principles of therapy are the same as for the haemophilia A patient.

PAEDIATRIC USE:

Dose is calculated according to body mass. Refer to the adult dose.

RECONSTITUTION:

USE ONLY THE INJECTION/INFUSION SET SUPPLIED AS **HAEMOSOLVATE FACTOR VIII** MUST BE ADMINISTERED VIA PLASTIC SYRINGES AND FILTERED BEFORE USE

1. Ensure that product and diluent are at room temperature (25 °C).
2. Remove the plastic cap from the stopper of the product vial and swab the exposed rubber stopper with a suitable antibacterial agent.
3. Attach the FILTER NEEDLE (short metal needle) to the syringe. This must remain attached until just before infusion.
4. Open the diluent and draw up 10 ml of Water for Injection (figure 1).



Figure 1

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

The vacuum will draw the diluent into the vial (figure 2). Rotate the vial to ensure complete wetting of the powder.

Do not use the product if no vacuum is present.



Figure 2

6. Gently swirl the vial until the powder is dissolved. Do not shake and avoid foaming. Reconstitution process should not take more than 30 minutes. Do not use if solution is turbid or contains particulate matter or if a gel forms after reconstitution.
7. 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 air vent needle.
8. Repeat the reconstitution process if more than one vial is used.
9. Withdraw the contents of the vial/s into the syringe (figure 3).



Figure 3

10. Remove the syringe and the filter needle from the vial/s. Invert the syringe, expel any air, then remove and discard the filter needle.
11. Attach the BUTTERFLY NEEDLE to the syringe (figure 4).



Figure 4

12. 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.

13. Discard any unused solution.

SIDE-EFFECTS

The following side effects may occur:

Skin and Appendages disorders: Less frequent: Urticaria, angioedema.

Central & Peripheral Nervous System disorders: Less frequent: Light-headedness.

Gastrointestinal disorders: Less frequent: Dry mouth, unpleasant taste, nausea or vomiting.

Vascular (extracardiac) disorders: Less frequent: Flushing.

Platelet, bleeding and clotting disorders:

Less frequent: Inhibitors may develop in specific patients, which neutralises the procoagulant activity of factor VIII and complicates replacement therapy.

Body as a whole –general disorders:

Less frequent: Fatigue, chills, headache.

Rare: Fever.

Less frequent: Allergic reactions or anaphylaxis may occur. In the event of acute anaphylactic shock, the injection must be stopped immediately and appropriate treatment initiated. (Refer to '**WARNINGS**').

Application site disorders: Less frequent: Burning, stinging or inflammation at the injection site.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Consequences of an overdosage are not known.

IDENTIFICATION

Lyophilised powder: a white or pale yellow friable powder or crystalline shell or plug.

Reconstituted solution: colourless, slightly opalescent solution, which may exhibit slight flocculation.

PRESENTATION

Haemosolvate Factor VIII 300 IU:

One vial of a sterile, white or pale yellow friable powder or crystalline shell or plug, containing 300 IU factor VIII in a clear glass, evacuated, 30 ml vial fitted with a rubber stopper and aluminium closure. One 10 ml Water for Injection, a reconstitution set, and an administration set is provided.

Haemosolvate Factor VIII 500 IU: (This product is available in 2 pack sizes):

500 IU: One vial of a sterile, white or pale yellow friable powder or crystalline shell or plug, containing 500 IU factor VIII in a clear glass, evacuated, 30 ml vial fitted with a rubber stopper and aluminium closure. One 10 ml Water for Injection, a reconstitution set, and an administration set is provided.

2 x 500 IU: Two vials of a sterile, white or pale yellow friable powder or crystalline shell or plug, each containing 500 IU factor VIII in a clear glass, evacuated, 30 ml vial fitted with a rubber stopper and aluminium closure. Two 10 ml Water for Injection, a reconstitution set, and an administration set is provided.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light.

Keep out of reach of children.

REGISTRATION NUMBERS

300 IU : 31/30.3/392

500 IU : Y/30.3/292

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

NATIONAL BIOPRODUCTS INSTITUTE

Company Reg. No. 1994/002044/08

NPO Reg. No. 020-898-NPO

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NAMIBIA S2

Reg. No.:

Haemosolvate Factor VIII 300 IU: 04/30.3/1047

Haemosolvate Factor VIII 500 IU: 04/30.2/1046