

For the use of Registered Medical Practitioner or a Hospital only

Reliplasma™

Plasma (Pooled and treated for virus inactivation) B.P.

Description

Reliplasma™ is a Solvent-Detergent treated plasma available as 100ml packs in A, B, O and AB blood groups. *Reliplasma™* contains plasma proteins and all coagulation factors, including the labile Factors V and VIII.

Composition

Reliplasma™ (SD treated) has the following composition

Volume	100 ml
Factor VIII	> 0.5 IU/ml
Factor V	> 0.5 IU/ml
Potassium	5mmol/l
Sodium	200mmol/l
PH	6.5 to 7.6

Plasma ABO Compatibility Chart

Recipient's blood group	Plasma, Donor's blood group
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

Although in routine circumstances Rh (D) positive plasma should not be given to Rh (D) negative women in the reproductive age group, SD plasma does not contain any intact red cells as contaminants since they are removed at various steps of manufacture. Red cell stroma if any at all is far less immunogenic than intact red cells, hence not a cause for concern.

Reliplasma™ has undergone several manufacturing steps that remove all red cell remnants; hence there is no Rh blood group specificity to be adhered to when it comes to making SD plasma transfusion decisions. No anti D prophylaxis is needed if this product is used in the reproductive age group.

Mechanism of Action

Reliplasma™ has same clinical activity as normal human FFP. *Reliplasma™* contains plasma proteins and all coagulation factors, including the labile Factors V and VIII. *Reliplasma™* is used to treat individuals who are actively bleeding.

Indications

- Active bleeding and multiple coagulation factor deficiencies as in:
 - Disseminated intravascular coagulation (DIC) : *Reliplasma™* is not indicated if there is no active bleeding associated with DIC.
 - Thrombotic Thrombocytopenic purpura (TTP)
 - Liver disease
 - Coagulopathy in massive transfusion
 - When specific factor deficiency cannot be or has not yet been identified
- Familial Factor V deficiency. If concentrated factor V is not available, *Reliplasma™* can be used as a source of Factor V.
- Deficiency of Factor II, VII, IX and X. If it is due to absence of Vitamin K or the use of drugs such as coumarin, like warfarin sodium and dicumarol that interfere with Vitamin K metabolism, administration of Vitamin K is preferred to Reliplasma in order to correct Vitamin K deficiency or Coumarin overdose. Because several hours are required for Vitamin K effectiveness, signs of haemorrhage may require transfusion of *Reliplasma™* in emergency situations.
- Antithrombin III deficiency
- Reliplasma™* should be used to replace single inherited clotting factor deficiencies, only if corresponding virus safe concentrates are not available.

Paediatric indications

Prematurity may predispose to longer clotting times but on its own is not an indication for plasma of any type. It should be noted that

the clotting times of normal infant blood are longer than those of adults; those of premature infants (with reduced protein synthesis by the liver) may be even longer even in the absence of further pathology (Male et al, 1999).

When haemorrhage due to HDN (Hemolytic disease of newborn) occurs, *Reliplasma™* (10-20 ml/kg) is indicated as well as intravenous vitamin K. Neonates with coagulopathy and bleeding can also start with a very small dose of plasma, to be monitored closely.

Neonates with significant coagulopathy, and risk of bleeding or who are about to undergo an invasive procedure, should receive approximately 15 ml/kg of *Reliplasma™* as well as a dose of vitamin. Shortening of the prolonged clotting times is unpredictable and should be checked following administration if necessary by laboratory support.

Relative contraindications

- Pregnant women, except at the time of delivery
- Polycythaemia in infancy
- Chronic hemolytic anemia
- Sickle cell disease
- Patient under going treatment with bone marrow damaging chemotherapy or radiation
- Bone marrow transplant patients

Absolute contraindication

- Disseminated intravascular coagulation without bleeding
- Reversal of warfarin anticoagulation in the absence of severe bleeding

Product Safety

The manufacturing process for *Reliplasma™* uses plasma collected from approved blood banks, where the donors are screened for their history and potential transfusion transmissible diseases, as per guidelines laid down by the regulatory authorities. Group specific minipools (12 units) of plasma are rescreened as per FDA guidelines before it is pooled into process batches.

The minipools are tested for HIV I & II antibodies, HBsAg by ELISA and HCV RNA by PCR. The final products are tested once again for HIV I & II, HBV, HCV and Parvovirus by PCR to ensure maximum safety from transfusion transmissible viruses.

The manufacturing procedure incorporates the well-known time tested and proven method of Solvent Detergent Technology, which inactivates lipid-coated viruses. Multiple steps have been employed in addition to solvent-detergent treatment such as, viral filtration to ensure product safety hence there is a very remote possibility that unknown infectious agent may be transmitted.

Solvent - Detergent inactivation method was validated with model viruses to study the efficacy of virus inactivation technology keeping in mind the process parameters, product characteristics and final product quality. The plasma is also passed through virus removal filter before sterile filtration.

Dosage and Administration

The dosage of *Reliplasma™* depends on clinical situations. The generally accepted starting dose is 10-15ml of plasma per kg body weight as an intravenous infusion. Additional dosage may be needed if patient has massive bleeding.

How much of SD plasma, [*Reliplasma™*] is used to treat a patient should be guided by timely tests of coagulation, including bed side tests. It should never be used as a simple volume replacement in adults or children.

Reliplasma™ is prepared from pools of plasma made from 100-200 donations. This pooling is useful in more than one way, some distinct advantages being pooling of antibodies, increasing the spectrum of antibodies, neutralization of antigens if any by antibodies

Handling of Frozen Product

Frozen plastic bags are brittle and vulnerable to damage particularly at the seams and at the attached tube remnants. So it is advisable to handle them with care.

Thawing of FFP, cryoprecipitate and cryosupernatant

Frozen plasma products must be thawed at 37° C (if thawed at 4° C, cryoprecipitate will form). There are several ways this can be achieved, the most common of them being usage of a circulating water bath.

- 1.1 Water bath carries a risk of bacterial contamination and must be maintained according to a controlled sterility protocol. Dry heating systems, which avoid denaturing the plasma proteins, are preferred. However, hospital and nursing homes are advised to use single good water baths with a good temperature control. The water has to be changed everyday taking care to ensure that the parts are not submerged during the thawing of frozen bags. Thus it is essential to place the primary SD *Reliplasma™* pack in an over-wrap bag to protect it from bacterial contamination. Once thawed, the primary pack should be removed from the over wrap bag and examined for leaks or damage. Damaged packs should not be used. Water baths used for thawing plasma must only be used for this purpose. They should be cleaned regularly (at least once a day) and filled with clean, laboratory grade water. Water bath use and maintenance schedules should be described by a specific standard operating procedure. All maintenance should be logged. The average time for 2 units to thaw is 20 min.

- 1.1.2 Dry ovens (temperature controlled fan-assisted incubator). These may have a lower potential for contaminating plasma packs with microbes, although they are usually of limited capacity. The time for thawing the plasma is usually 10 min for 2 units.

- 1.1.3 Microwave ovens. Although these defrost in 2 - 3 min, they have the disadvantage of being expensive and of limited capacity. There are also concerns over the creation of 'hot spots' in the packs.

Storage after thawing

Thawed plasma should be kept at 4°C if there is any delay in transfusion. Current UK guidelines (United Kingdom Blood Transfusion Services / National Institute for Biological standards and Control, 2002), require transfusion within 4 hours, whereas the American Association of Blood Banks (2002) allow a delay of up to 24 hours. The FVIII activity in plasma will decline after 24 hours at 4°C by up to 28%, but all other factors remain stable for 5 days showing that storing FFP for up to 72 hours after thawing caused about 40% of the FVIII activity to be lost, although the FVIII activity and fibrinogen content were still substantially higher than in the cryosupernatant fraction. They recommended that plasma stored for up to 72 hours (at 4°C) after thawing can be used like cryosupernatant plasma when FVIII replacement is not required. Another concern is safety from contamination with micro-organisms that as indicated elsewhere in this product insert may be introduced during thawing, particularly if a water bath is used and thawed product is maintained for that long at 4°C. Proper protocols and documentation, and a method of thawing which does not rely on immersion in water, will reduce this risk. Therefore, further study is needed before post-thaw storage beyond 24 hours could be recommended.

After thawing, and when FVIII replacement is not required, SD Plasma may be stored at 4°C in an approved blood storage refrigerator before administration to the patient so long as the infusion is completed within 24 hours of thawing.

Control of issue and transfusion

As for all blood components, *Reliplasma™* should be administered to adults and children only after passing through a 170-200 µ filter, as provided in standard transfusion sets.

Response to *Reliplasma™* transfusion

Responses should be monitored, as they will serve as a guide to further supportive care. If plasma is given because the patient is bleeding, the clinical response may well be the best indication of effectiveness of transfusion. If plasma is given to correct abnormal coagulation parameters, the degree of correction should be recorded. Monitoring may be through measuring coagulation activities by traditional laboratory techniques, or through various 'near-patient' testing devices; the chosen methods should be timely and must suit the clinical situation.

Adverse Reactions

The following adverse reactions are known to be associated with routine screened FFP and therefore could also occur with *Reliplasma™*:

- Acute severe allergic reactions (characterized by e.g. flushing of the skin, hypotension, substernal pain, bronchospasms, dyspnoea, and cardio-respiratory collapse) due to hypersensitivity to infused proteins or anti-IgA
- Transfusion-related acute lung injury (TRALI) characterized by chills, fever, a non-productive cough, and dyspnoea due to hemolysis from transfused antibodies to blood group antigens especially A and B.
- Passive post-transfusional purpura (PTP) characterized by dyspnoea, rash, fever, generalized purpura, and marked thrombocytopenia.
- Citrate toxicity (e.g. fatigue, paresthesia, tremor, and hypocalcemia) especially in patients with liver function disorder due to high infusion rate.

Warning and Precautions

Reliplasma™ should be used with caution under the following conditions:

- Previous reactions to FFP / Blood products
- Manifest or latent cardiac decompensation.
- Pulmonary oedema.
- IgA deficiency.
- Plasma protein allergy.
- Reliplasma™* is used in patients with unestablished coagulation factor deficiency / bleeding diathesis.
- Reliplasma™* should be used in cases of bleeding caused by von Willebrand's Disease (vWD) or other coagulation factor deficiencies, only if specific factor concentrate is not available.

Pregnancy and Lactation

Animal reproduction studies have not been conducted with *Reliplasma™*. It is also not known whether *Reliplasma™* can cause foetal harm when administered to pregnant or lactating women or can affect reproduction capacity. Hence *Reliplasma™* should be given only if alternative therapies are unavailable.

Storage and Shelf Life

The shelf life of *Reliplasma™* is 2 years when stored at 30°C or lower and protected from light.

Infusion Instructions

- ABO-blood group compatibility is a must for administration of *Reliplasma™*
- In emergency cases, *Reliplasma™* of AB blood group can be regarded as universal plasma since it can be given to all patients
- Thaw at 37°C
- Do not exceed 37°C
- Do not immerse in hot water bath
- Infuse within 4 hours of thawing
- Reliplasma™* must be thawed using a technique that avoids risk of bacterial contamination
- Plastic packs containing any of these plasma products are brittle in the frozen state and must be handled with care
- Discard leftover or unused *Reliplasma™* if any
- It is advisable to use blood transfusion filter during infusion
- Do not infuse if visible clot is observed
- Do not use if turbid or discolored (green)
- Avoid vigorous shaking
- Reliplasma™* bags should not be refrozen after thawing
- Patients should be observed for at least 20 minutes after the administration.
- In case of anaphylactic reaction or shock, the infusion must be stopped immediately.

References

- Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant (bjh guideline) 2004 The British Society for Haematology, 126, 1128 2004 doi:10.1111/j.1365-2141.2004.04972.x
- Guideline for the use of fresh frozen plasma. Medical Directors Advisory Committee, National Blood Transfusion Council. S. African Medical Journal. 1998 Oct;88(10):1344-7
- Solvent/Detergent-Treated Plasma: A Virus-Inactivated Substitute for Fresh Frozen Plasma By Bernard Horowitz, Richard Bonomo, Alfred M. Prince, Sing N. Chin, Betsy Brotman, and Richard W. Shulman Blood, Vol79, No 3 (February I), 1992: pp 826-831

Glossary

- FFP: Fresh Frozen Plasma
- 1 unit: 1 unit of plasma is plasma derived from 350 ml to 450 ml of whole blood
- Minipool: Amount of group specific plasma from 12 units from different donors
- HCV: Hepatitis C Virus
- HBV: Hepatitis B Virus
- HIV: Human Immunodeficiency Virus
- HBsAg: Hepatitis B surface antigen
- ELISA: Enzyme linked Immunosorbent assay

Manufactured by



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