PRESCRIBING INFORMATION

LMD 10 % in Dextrose 5%
(Dextran 40 in Dextrose Injection USP)

Dextran 100 mg/mL and Dextrose 50 mg/mL

LMD 10% in 0.9% Sodium Chloride
(Dextran 40 in Sodium Chloride Injection USP)

Dextran 100 mg/mL and Sodium Chloride 9 mg/mL

Sterile Solution

Replacement preparations

Pfizer Canada Inc,
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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In shock: Expands plasma volume and enhances microcirculation blood flow

For use in impairment of arterial or venous circulation

In extracorporeal circulation: To prime pump oxygenator

NOTE

Certain sugar-containing solutions, particularly those with electrolytes, may develop a yellowish colour.

This colour does not affect their quality or efficacy. This refers to colour of solution, not clarity.

Solutions which are not clear should not be used.

Plasma Volume Expander

LMD 10% in Dextrose 5% and LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Dextrose or Sodium Chloride Injection USP) is a preparation of low molecular weight dextran which has an average molecular weight of approximately 40 000. It also has been referred to as low viscous or low viscosity dextran. LMD 10% in Dextrose 5% and LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Dextrose or Sodium Chloride Injection USP) are offered as a 10% w/v solution in either 0.9% sodium chloride, or 5% dextrose in water.

Dextran 40 is prepared by acid hydrolysis and differential fractionation of a crude macromolecular polysaccharide produced from the fermentation of sucrose by the bacterium *Leuconostoc mesenteroides* (strain B-512). The crude material is composed of linked age molecular weight ranging from 10 000 to 90 000 (average approximately 40 000) when measured by a light-scattering method. More than 90% of the cross linkages are of the α-1,6 glycosidic, straight chain type.

ACTION

The fundamental action of LMD 10% in Dextrose 5% and LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Dextrose or Sodium Chloride Injection USP) is the enhancement of blood flow, particularly in the microcirculation. This enhancement is due to:

1. Its primary effect of volume expansion with resultant hemodilution;
2. Maintenance of the electronegativity of red blood cells;
3. Coating of red blood cells and platelets;
4. Increase in the suspension stability of blood;
5. Decrease in the viscosity of blood;
6. Decrease in blood levels of fibrinogen.

It should be emphasized that the above effects are not exerted separately, but conjointly they result in the enhancement of blood flow.

Experimental studies in animals have shown that dextran 40:

1. When used in the treatment of shock, quickly restores reduced intravascular volume and produces increases in cardiac index of up to 150% of control. It prevents or lessens intravascular hemagglutination (blood sludging and cell aggregation) as evidenced by direct and photographic visualization of the mesenteric circulation.
2. During prolonged periods of pump-oxygenator perfusion in extracorporeal circulation, it acts to enhance blood flow in the microcirculation and maintains normal distribution of blood flow in the kidney, sustains circulatory volume and flow, prevents or reduces the occurrence of microinfarcts in the liver, kidney and myocardium, and prevents or diminishes denaturation of plasma protein.

Clinical reports have shown that LMD 10% products:

1. When used in the treatment of shock, produces significant increases in blood volume, central venous pressure, cardiac output, stroke volume, blood pressure, and urinary output. They reduce blood viscosity, peripheral resistance, and improves peripheral blood flow with the release of sequestered blood cells, thereby increasing venous return to the heart.
2. When used as part of the pump prime for extracorporeal procedures, LMD 10% products, as compared to whole blood, 5% albumin, or whole blood plus 5% dextrose in water, lead to less destruction of red blood cells and platelets, reduce intravascular hemagglutination and maintain erythrocyte electronegativity.

Plasma concentrations of dextran 40 vary with the rate of infusion, total amount administered, and rate of disappearance from the plasma. During infusion, dextran 40 is evenly distributed in the vascular system; after infusion the plasma concentration falls rapidly during the first hour and thereafter more slowly. Its distribution according to molecular weight shifts toward higher molecular weights as the smaller molecules are excreted by the kidney. Following infusion in normovolemic subjects, approximately 50% is excreted within 3 hours, 60% is excreted within 6 hours and about 75% within 24 hours.

A portion of infused dextran is excreted into the gastrointestinal tract and eliminated in the feces. Reabsorption of dextran by the renal tubules is negligible. The unexcreted molecules of dextran diffuse into the extravascular compartment and are temporarily taken up by the reticuloendothelial system. Some of these molecules are returned to the intravascular

compartment via the lymphatics. Dextran is slowly degraded by the enzyme dextranase to glucose.

In dogs the acute intravenous LD_{50} of a 10% dextran 40 solution in sodium chloride ranges from 10 to 15 g/kg. In mice the intravenous LD_{50} ranges from 14 to 16 g/kg. In rats, dextran 40 was not lethal at intravenous doses up to 12 g/kg.

INDICATIONS

LMD 10% in Dextrose 5% and LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Dextrose or Sodium Chloride Injection USP) are indicated:

1. In the treatment of shock (hemorrhagic, cardiogenic, septic), for expansion of plasma volume and enhancement of blood flow. They are intended as an adjunct, and its use, therefore, does not negate the need for other methods of treatment including adequate fluid and electrolyte therapy in addition to LMD 10% products.
2. As priming fluids in pump-oxygenators for perfusion during extracorporeal circulation. For this purpose, LMD 10 % products can be used either as the sole priming fluid or as an additive to other priming fluids.
3. In impairment of the arterial and venous circulation as in thrombosis, thrombophlebitis, imminent gangrene, ulcus cruris and Raynaud's disease.

CONTRAINDICATIONS

LMD 10% in Dextrose 5% and LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Dextrose or Sodium Chloride Injection USP) are contraindicated in the presence of marked thrombocytopenia, hypofibrinogenemia and in renal disease with severe oliguria or anuria.

WARNINGS

Because LMD 10% in Dextrose 5% and LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Dextrose or Sodium Chloride Injection USP) are hypertonic colloid solutions, they attract water from the extravascular space. This shift of fluid should be considered if the drug is used for poorly hydrated patients where additional fluid therapy will be needed. If LMD 10% product is given in excess, vascular overload could occur. The latter possibility can be avoided with careful clinical monitoring, preferably by central venous pressure.

Renal excretion of dextran 40 causes elevation of the specific gravity of the urine. In the presence of adequate urine flow, only minor elevations will occur, whereas in patients with reduced urine output, urine viscosity and specific gravity can be increased markedly. Since urine osmolarity is only slightly increased by the presence of dextran molecules, it is recommended that, when desired, a patient's state of hydration be assessed by determination of urine or serum

osmolarity. If signs of dehydration are present, additional fluid should be administered. An osmotic diuretic such as mannitol also can be used to maintain an adequate urine flow.

Although numerous studies attest to the "nephrotonic" effect of dextran 40, renal failure has been reported to occur after the use of dextran 40. While the pre-existing clinical condition may have accounted for the occurrence of oliguria or anuria in these cases, it is possible that the administration of dextran 40 was contributory.

Evidence of tubular vacuolization (osmotic nephrosis) has been found following dextran 40 administration in animals and man. While this appears to be reversible experimentally in animals and to be a consequence of high urine concentration of the drug, it has not been shown to occur with clinical use and its exact clinical significance is presently unknown.

Occasional abnormal renal and hepatic function values have been reported following administration of dextran 40. However, the specific effect of dextran 40 on renal and hepatic function could not be determined because most of the patients also had undergone surgery or cardiac catheterization. A comparative study of dextran 40 and 5% dextrose in water as pump-priming fluids in open-heart surgery, has shown similar elevations of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) values in both groups.

PRECAUTIONS

In recommended doses, LMD 10% in Dextrose 5% and LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Dextrose or Sodium Chloride Injection USP) have no significant effect on the coagulation of blood. Although it is recommended that not more than 1500 mL should be administered within a 24-hour period, doses up to 2000 mL have been used in the treatment of shock and this amount has been shown not to increase bleeding nor to have any effects upon coagulation. Controlled series comparing pump primes with and without LMD 10% products in extracorporeal circulation have shown similar findings. However, dosages exceeding those recommended may cause a prolongation of bleeding time. This may be only a reflection of improved microcirculatory perfusion, since increased bleeding time following administration of dextran 40 has been noted in the absence of alteration of any coagulation factor. Therefore, the physician should be aware of the possibility of slightly increased blood loss.

Dextrans of higher molecular weight can, by themselves, produce erythrocyte aggregation which might interfere with blood-typing and cross-matching.

Evidence is also available which suggests that difficulty may be encountered when proteolytic enzyme techniques are used to match blood. It is recommended that samples for cross-matching be withdrawn before infusion of LMD 10% product has begun.

Blood sugar determinations that involve sulfuric acid hydrolysis may give higher values in patients receiving dextran 40. Also, laboratory tests which depend on turbidimetric measurements of the serum may be falsely elevated by the presence of dextran. Thus,

consideration should be given to withdrawal of blood for chemical laboratory tests prior to initiating therapy.

ADVERSE REACTIONS

Antigenicity of dextrans is directly related to their degree of branching. Since LMD 10% products have a new low degree of branching, they are relatively free of antigenic effect. However, a few individuals have experienced mild urticarial reactions to dextran 40 infusion. More severe reactions, consisting of generalized urticaria, tightness of the chest, wheezing, hypotension, nausea and vomiting may occur in rare instances. Symptoms and signs of adverse systemic reaction may be relieved by parenteral administration of antihistamines, ephedrine or epinephrine, while other means of shock therapy are instituted. The route of administration and dosages of the therapeutic agent selected will depend upon the severity and rapidity of progression of the reaction.

ADMINISTRATION AND DOSAGE

LMD 10% in Dextrose 5% and LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Dextrose or Sodium Chloride Injection USP) are administered by intravenous infusion only.

1. In shock with large volume blood loss, 500 to 1000 mL of a 10% solution (50 to 100 g) may be given as rapidly as necessary to effect improvement. When large volume losses are not evident or in cases of cardiogenic shock or septic shock, it is recommended that not more than 500 mL be given in a one hour period. Initial therapy with LMD 10% product may be followed by another 500 mL during the ensuing 4 to 8 hours. Total dosage should not exceed 1500 mL in 24 hours in an acute situation. If, for any reason, LMD 10% product is to be administered over a period of days, dosage should not exceed 500 mL per day.
2. In extracorporeal perfusion, the dosage of LMD 10% products used will vary with the volume of the pump-oxygenator. LMD 10% products can serve as sole primer or as an additive to other priming fluids. Generally, 10 to 20 mL of a 10% solution (1 to 2 g) of dextran 40 per kilogram of body weight is added to the perfusion circuit. Usually, total dosage should not exceed 2 g/kg of body weight.

Do not administer unless solution is clear and container is undamaged. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Do not use if crystallization has occurred.

Note: When infusing concentrated LMD, the administration set should include a 0.2 micron filter.

HOW SUPPLIED

LMD 10% in 0.9% Sodium Chloride

LMD 10% in 0.9% Sodium Chloride (Dextran 40 in Sodium Chloride Injection USP) is supplied as a sterile, non-pyrogenic solution of dextran 40 in 0.9% sodium chloride, in 500 mL flexible PVC containers (DIN 00224227). Each 500 mL contains dextran 40, 50 g, and sodium chloride, 4.5 g (77 mEq sodium [Na+] and chloride [CI-]). The solution does not contain a buffer; its pH ranges from 3.5 to 7.0, adjusted with sodium hydroxide and/or hydrochloric acid.

LMD 10% in Dextrose 5%

LMD 10% in Dextrose 5% (Dextran 40 in Dextrose Injection USP) is supplied as a sterile, non-pyrogenic solution of dextran 40 in 5% dextrose, in 500 mL flexible PVC containers (DIN 00224235). Each 500 mL contains dextran 40, 50 g and dextrose 25 g. The solution does not contain a buffer; its pH ranges from 3.0 to 7.0. The solution is salt-free, and suitable for patients requiring low sodium intake.

LMD 10% products should not be used unless the solution is crystal clear. The solution has a tendency to form flakes when subjected to temperature variations. Storage should be at a constant temperature, preferably between 20 and 25°C (see “Controlled Room Temperature” in USP). If flakes of dextran appear, they can be dissolved by heating in a water bath (at 100°C), or in an autoclave. Autoclaving for approximately 15 minutes (at 110°C) is usually sufficient to dissolve the flakes.

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Pfizer Canada Inc.
Kirkland, Québec
H9J 2M5