PRODUCT MONOGRAPH

PENTASPAN*

(10% Pentastarch in 0.9% Sodium Chloride Injection)

Injection

Plasma Volume Expander

Bristol-Myers Squibb Canada
Montreal, Canada

* TM auth. user
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THERAPEUTIC CLASSIFICATION

Plasma Volume Expander

ACTION AND CLINICAL PHARMACOLOGY

The colloidal properties of pentastarch render it useful as a plasma volume expander. Intravenous infusion of PENTASPAN (pentastarch) results in expansion of the plasma volume in excess of the volume infused. This expansion persists for approximately 18 to 24 hours and is expected to improve the hemodynamic status for 12 to 18 hours.

Pentastarch molecules below 50,000 molecular weight are rapidly eliminated by renal excretion. A single dose of approximately 500 mL of PENTASPAN results in elimination in the urine of approximately 70% of the dose within 24 hours, and approximately 80% of the dose within one week. The remaining percentage of the administered dose is presumed to be eliminated at a slower rate. Although this process is variable, it generally results in an intravascular pentastarch concentration below the level of detection by one week. The hydroxyethyl group is not cleaved, but remains intact and attached to glucose units when excreted.

INDICATIONS AND CLINICAL USE

PENTASPAN (pentastarch) is indicated when plasma volume expansion is desired as an adjunct in the management of shock due to hemorrhage, surgery, sepsis, burns or other trauma. It is not a substitute for red blood cells or coagulation factors in plasma.

CONTRAINDICATIONS

PENTASPAN (pentastarch) is contraindicated in patients with sepsis.

PENTASPAN is contraindicated in patients with severe liver disease.

PENTASPAN is contraindicated in patients with known hypersensitivity to hydroxyethyl starch, or with bleeding disorders, or with congestive heart failure where volume overload is a potential problem. PENTASPAN should not be used in renal disease with oliguria or anuria not related to hypovolemia.

WARNINGS

Serious Warnings and Precautions

In patients with hypovolemia requiring intensive or emergent care, a careful evaluation of the risk of sustaining renal injury or liver failure should be undertaken before instituting treatment with PENTASPAN. The use of crystalloid solutions in preference to PENTASPAN should be considered in patients deemed at risk of these adverse reactions.

General

Administration of large volumes of PENTASPAN (pentastarch) will decrease haemoglobin concentration and dilute plasma proteins excessively. Administration should be kept below the recommended ceiling of 2000 mL in 24 hours (see Dosage and Administration).

As with other plasma volume expanders, large volumes of PENTASPAN will alter the coagulation mechanisms in as much as a prolongation of prothrombin, partial thromboplastin and clotting times will occur. The physician should also be alert to the possibility of transient prolongation of bleeding time.

Hypersensitivity has been seen (wheezing, urticaria and hypotension). Anaphylactic/ anaphylactoid reactions have been reported with PENTASPAN; a causal relationship has not been established. If hypersensitivity effects occur, discontinue the drug and, if necessary, administer appropriate therapy.

Immume

Anaphylactoid reactions (mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema) have been reported with solutions containing hydroxyethyl starch.

Use in Pregnancy

PENTASPAN has been shown to be embryocidal in New Zealand rabbits and in Swiss mice when given in doses 5 times the human dose. There are no adequate and well-controlled clinical studies using pentastarch in pregnant women. PENTASPAN should not be used during pregnancy unless potential benefits justify the potential risk to the fetus.

Nursing Mothers

It is not known whether pentastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PENTASPAN is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of PENTASPAN in children have not been established.

PRECAUTIONS

PENTASPAN (pentastarch), like all plasma volume expanders, is not a substitute for red blood cells or coagulation factors in plasma.

The possibility of circulatory overload should be kept in mind.

Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal route by which pentastarch is eliminated.

The serum chemistries of sixteen normal volunteers who were given PENTASPAN in doses of 500 to 2000 mL (2x1000mL infusions on separate days) were essentially unchanged from pre- to seven days post-infusion, except for dilutional effects. There were no clinically significant abnormal values except for one creatinine phosphokinase level following an episode of venospasm. However, indirect bilirubin levels of 8.3 mg/L (normal 0 - 7 mg/L) have been reported in 2 out of 20 normal subjects who received multiple infusions of a 6% hetastarch product. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering PENTASPAN to patients with a history of liver disease.

Caution should be exercised when administering PENTASPAN to patients allergic to corn because such patients can also be allergic to PENTASPAN.

Elevated serum amylase levels may be observed temporarily following administration of PENTASPAN although no association with pancreatitis has been demonstrated. A 6% hetastarch injection product has not been shown to increase serum lipase. Similar effects may be expected with PENTASPAN.

ADVERSE REACTIONS

Coagulation disorders or hemorrhage have been reported in association with the use of PENTASPAN(pentastarch) as a plasma volume expander. Headache, diarrhea, nausea, weakness, temporary weight gain, insomnia, fatigue, fever, edema, paresthesia, acne, malaise, shakiness, dizziness, chest pain, chills, nasal congestion, anxiety, and increased heart rate have also been reported in clinical studies involving PENTASPAN.

It is uncertain whether any of these adverse experiences are attributable to the drug, medical procedures, concurrent adjunctive medication, or a combination of these factors.

Hypersensitivity has been seen (wheezing, urticaria and hypotension).
Anaphylactic/anaphylactoid reactions have been reported with PENTASPAN (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The treatment of overdosage of PENTASPAN (pentastarch) would be essentially symptomatic

and supportive.

DOSAGE AND ADMINISTRATION

PENTASPAN (pentastarch) is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost. In adults, the amount usually administered is 500 to 2000 mL. Total dosage does not usually exceed 2000 mL per day or approximately 28 mL per kg of body weight for the typical 70 kg patient. In acute hemorrhagic shock, an administration rate approaching 20 mL per kg per hour may be used. Use beyond 72 hours has not been studied.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

The solution is intended for intravenous administration using sterile equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Pentastarch (USAN)

Chemical Name: Low molecular weight, low molar substitution hydroxyethyl starch

Structural Formula:

Amylopectin derivative in which R_2, R_3, and R_6 are H or CH_2CH_2OH, or R_6 is a branching point in the starch polymer connected through a 1-6 linkage to additional α-D-glucopyranosyl units.

Average Molecular Weight: 200,000 - 300,000

Pentastarch is an artificial colloid derived from a waxy starch composed almost entirely of amylopectin. Hydroxyethyl ether groups are introduced into the glucose units of the starch and the resultant material is hydrolyzed to yield a product with a molecular weight suitable for use as a plasma volume expander. Pentastarch is characterized by its molar substitution, and also by its molecular weight.

The degree of substitution is 0.40 - 0.50 which means pentastarch has approximately 45 hydroxyethyl groups for every 100 glucose units. The average molecular weight of pentastarch is 200,000 - 300,000. Hydroxyethyl groups are attached by an ether linkage primarily at C-2 of the glucose unit and to a lesser extent at C-3 and C-6. The polymer resembles glycogen, and the polymerized glucose units are joined primarily by 1-4 linkages with occasional 1-6 branching linkages. The degree of branching is approximately 1:20 which means that there is one 1-6 branch for every 20 glucose polymer units.

Composition

PENTASPAN is supplied sterile and nonpyrogenic in 250 and 500 mL plastic, intravenous infusion bags. The composition of each 100 mL is as follows:

Pentastarch	10.0 g
Sodium Chloride USP	0.9 g
Water for Injection USP	qs
pH adjusted with Sodium Hydroxide	

Approximate Concentration of Electrolytes (mEq/Litre): Sodium 154, Chloride 154

pH: Approx. 5.0

Calculated osmolality: Approx. 326 mOsm/Kg

Stability and Storage

PENTASPAN is supplied sterile and nonpyrogenic in 250 mL and 500 mL plastic, intravenous infusion bags. Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (15-25°C).

PENTASPAN is a clear, pale yellow to amber solution. Exposure to prolonged adverse storage conditions may result in a change to a turbid deep brown or the formation of a crystalline precipitate. Do not use the solution if these conditions are evident.

Special Instructions

Caution - Before administering to patient, review these directions:

Visual Checking

1. Do not remove the plastic infusion container from its overwrap until immediately before use.
2. While the overwrap is intact, identify the solution (PENTASPAN), lot number and expiration date.
3. Check that the solution is clear.
4. Inspect the intact unit for signs of obvious damage. If present, the unit should not be used.

Removal of Overwrap

A peelable area is located in the lower right hand corner of the unit (the label facing upward and the port facing downward). Pull apart the two edges. You can also tear at any notch located at either end of the unit. After removing overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

Preparation for Administration (Use aseptic technique)

1. Close flow control clamp of administration set.
2. Twist off plug from port designated "Infusion Set Port".
3. Insert spike of infusion set into port with a twisting motion until the set is firmly sealed.
4. Suspend container from hanger.
5. Follow manufacturer's recommended procedures for the administration set.
6. Discontinue administration and notify physician immediately if patient exhibits signs of adverse reactions.

DOSAGE FORMS

Availability

PENTASPAN (pentastarch) is supplied sterile and nonpyrogenic in 250 mL and 500 mL plastic, intravenous infusion bags.

PHARMACOLOGY

In a clinical study using pentastarch as an erythrocyte sedimenting agent in leukapheresis, a number of pharmacokinetic parameters were evaluated. In the leukapheresis procedure, 500 mL of pentastarch (10% in 0.9% NaCl) were added to the input line of the cell separator in a 1:13 ratio with whole blood. The elimination half-life, area under the curve (AUC) and renal clearance were measured at selected times pre-, during and post-treatment. The results indicated that elimination of approximately 70% of the dose occurred within 24 hours and approximately 80% within one week. The half-life measured over the seven-day period was 1.9 ± 0.5 days. This rapid elimination of pentastarch decreases the potential for accumulation after repeated dosing.

In a second pharmacokinetic study, pentastarch (10% in 0.9% NaCl) was administered as a single intravenous infusion of 500 mL over 30 minutes. Plasma volume was measured directly by the ^{125}I human serum albumin technique and indirectly from total protein and albumin levels and from hematocrit and hemoglobin determinations. Assessments were conducted pre-treatment and at specified intervals during the 24 hours after infusion of pentastarch. Plasma and urine specimens were collected prior to treatment and at frequent intervals up to 24 hours after infusion. Pentastarch was assessed by determining total carbohydrate in plasma and urine.

As measured by ^{125}I albumin there was a statistically significant increase over baseline plasma volume by one hour post pentastarch infusion which endured for six hours. Measurement by the protein/albumin method revealed a significant increase over baseline plasma volume immediately after infusion which continued for the duration of the follow-up period (24 hours). Similar results were evident when plasma volume was estimated by the hematocrit/hemoglobin method. Elevation of plasma volume over baseline levels endured for 9 hours post administration. Following pentastarch administration, an immediate and consistent decline in plasma concentration was also observed. The cumulative excretion of pentastarch reflects the finding, such that 24 hours after administration, 72% of the dose was accounted for by urinary hydroxyethyl starch.

TOXICOLOGY

In addition to the following toxicology studies, pentastarch did not demonstrate mutagenicity in the Salmonella (Ames) Test or the Mouse Micronucleus Test.

Species	Route	Test Article	No. & Sex	Dose	Dose Duration	Parameters Evaluated	Significant Observations and Conclusions
ACUTE TOXICITY							
Mouse	I.V.	Pentastarch	10F, 10M 10F, 10M 10F, 10M 10F, 10M 10M	14.4 g/kg 17.3 g/kg 20.8 g/kg 25.0 g/kg 12.0 g/kg	Single Dose	Clinical observations and mortality during two weeks following administration.	LD_{50} (female) = 19.8 g/kg LD_{50} (male) = 18.1 g/kg
SUBACUTE TOXICITY							
Rabbit	I.V.	Control saline	5F, 5M 5F, 5M 1F, 1M	15 mL/kg/day 40 mL/kg/day 80 mL/kg/day	5 days/ week for 4 weeks	Clinical observation, body weight, mortality, hematology serum biochemistry, urinalysis, function tests, carbohydrate levels. Macroscopic and microscopic study of organs, organ weight. Determination of total lipids, phospholipids, triglycerides, cholesterol and polysaccharides in the liver.	Pentastarch produced a slight decrease in plasma fibrinogen and increases in serum glucose and amylase levels. The latter changes were related to metabolism of pentastarch. Microscopically, the presence of highly vacuolated macrophages was observed in several tissues, especially those of the reticulo-endothelial system. Similar administration of 80 mL/kg proved lethal in all rabbits within the first week of treatment.
		Pentastarch 10%	5F, 5M 5F, 5M 1F, 1M	15 mL/kg/day 40 mL/kg/day 80 mL/kg/day			
		Hetastarch 6%	5F, 5M 5F, 5M 1F, 1M	15 mL/kg/day 40 mL/kg/day 80 mL/kg/day			
		Dextran 40	5F, 5M 5F, 5M 1F, 1M	15 mL/kg/day 40 mL/kg/day 80 mL/kg/day			
		Rheomacrodex	5F, 5M 5F, 5M 1F, 1M	15 mL/kg/day 40 mL/kg/day 80 mL/kg/day			

Species	Route	Test Article	No. & Sex	Dose	Dose Duration	Parameters Evaluated	Significant Observations and Conclusions
SUBACUTE TOXICITY (Cont'd)							
Dog	I.V.	Control saline Pentastarch 10% Rheomacrodex	2F, 2M 2F, 2M 2F, 2M	40 mL/kg/day 40 mL/kg/day 40 mL/kg/day	6 days/ week for 3 weeks	Clinical observation, food intake, body weight, hematology, serum biochemistry, urinalysis, function tests, macroscopic and microscopic examination of organs.	Pentastarch produced only several instances of vomiting and diarrhea and slightly elevated relative kidneys weight. Microscopically, small islands of disseminated fatty degeneration in the liver and discrete vacuolization of some renal cells were observed in two females. Additionally, one female demonstrated signs of fibrohyperplastic mastopathy.
Dog	I.V.	Saline control Pentastarch 10% Dextran 40	3F, 3M 6F, 6M 3F, 3M	45 mL/kg/day 45 mL/kg/day 45 mL/kg/day	5 consecutive days followed by 2 dose-free days. Cycle repeated 4 times for a total duration of 28 days.	Clinical observation, vital signs, blood biochemistry, serum amylase, hematology, coagulation, serum polysaccharide, plasma albumin, hemoglobin, hematocrit, oncotic pressure and plasma volume. ^{131} I-labelled human serum albumin was used to determine plasma volume. Necroscopy.	Uptake and storage by liver of pentastarch was reversible and no permanent pathological changes were caused by pentastarch administration.
Mouse	I.V.	Saline Control Pentastarch 10% Dextran 40	5F, 5M 5F, 5M 5F, 5M	50 mL/kg/day 50 mL/kg/day 50 mL/kg/day	14 consecutive days	Blood analysis; necroscopy.	Uptake and storage of pentastarch by the liver was reversible.

Species	Route	Test Article	No. & Sex	Dose	Dose Duration	Parameters Evaluated	Significant Observations and Conclusions
TERATOLOGY							
Rabbit	I.V.	Saline control Pentastarch 10% Pentastarch 10% Pentastarch 10%	12F 12F 12F 12F	40 mL/kg/day 10 mL/kg/day 20 mL/kg/day 40 mL/kg/day	Daily from days 6 to 18 of gestation	Maternal observations: Daily observation for toxic effects and mortality; body weights taken periodically through gestation. Sacrifice of dose on Day 29 of gestation followed by cesarean delivery. Postmortem examination: Weight and examination of uterus; number of dead and live fetuses; number of implants; number of resorption sites. Fetal examination: viability; number and weight; visceral, skeletal and organ examinations.	The intravenous administration of pentastarch at 10 and 20 mL/kg/day, during organogenesis, does not result in teratogenesis or embryotoxicity. However, at 40 mL/kg/day, pentastarch seems to increase the number of resorptions and minor visceral anomalities.
Mouse	I.V.	Saline control Pentastarch 10% Pentastarch 10% Pentastarch 10%	20F 20F 20F 20F	40 mL/kg/day 10 mL/kg/day 20 mL/kg/day 40 mL/kg/day	Daily from days 6 to 15 of gestation	Maternal observation: Daily observation for toxic effects and mortality; body weights taken periodically through gestation. Sacrifice of dams on Day 20 of gestation since litters had been unexpectedly delivered on Day 19. Postmortem examination: Weight and examination of uterus; number of dead and live fetuses; number of resorption sites.	Pentastarch is not teratogenic or embryotoxic in doses up to 40 mL/kg/day. At the high dose pentastarch diminished nidation.

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