a pH of 7.8. Less than 5% of the hemoglobin are as unstabilized tetramers, and approximately 50% have a molecular weight between 65 and 130 kD, with no more than 10% having a molecular weight >500 kD. The product contains less than the detectable level of 3.5 mcg/mL free-glutaraldehyde and 0.05 EU/mL, endotoxin.

Storage/Stability/Compatibility

The product remains stable at room temperature or refrigerated (2°–30°C) for up to 3 years; expiration date is printed on the bag. Outdated product is not returnable. Do not freeze. It must remain in its over wrap during storage; once removed, it should be used within 24 hours. The foil over wrap serves as an oxygen barrier, protecting the hemoglobin from conversion to methemoglobin.

The manufacturer states that *Oxyglobin*® is physically **compatible** with any other IV fluid, but should not be mixed with other solutions or medications in the bag; other intravenous solutions and medications may be administered via a separate site and line, however.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Hemoglobin Glutamer-200 (bovine) in 60 mL and 125 mL ready to use infusion bags; *Oxyglobin*® (Biopure); (Rx). Approved for use in dogs.

The ARCI (Racing Commissioners International) has designated this drug as a class 2 substance. It is prohibited to be at racing premises. See the appendix for more information.

HUMAN-LABELED PRODUCTS: None in USA at present

HEPARIN SODIUM
HEPARIN CALCIUM

(***hep***-ah-rin)

ANTICOAGULANT

Prescriber Highlights

- Parenteral anticoagulant used primarily for treatment of DIC (use controversial) & thromboembolic disease
- Contraindications: Known hypersensitivity, severe thrombocytopenia, or uncontrollable bleeding (caused by something other than DIC)
- Adverse Effects: Most common are bleeding & thrombocytopenia
- Protamine may reverse effects
- Intensive monitoring required

Uses/Indications

Heparin's primary uses in small animal medicine has included treatment of Disseminated Intravascular Coagulation (DIC) and prophylaxis of thromboembolic disease. In horses, it has been used in the treatment of DIC and as prophylactic therapy for laminitis (unproven efficacy).

Use for treating DIC has become increasingly controversial. The most recent evidence suggests that heparin not be used during DIC in patients with concurrent inflammatory processes.

Pharmacology/Actions

Heparin acts on coagulation factors in both the intrinsic and extrinsic coagulation pathways. Low concentrations of heparin when combined with antithrombin III inactivate factor X_a and prevent the conversion of prothrombin to thrombin. In higher doses, heparin inactivates thrombin, blocks the conversion of fibrinogen to fibrin and when combined with antithrombin III inactivates factors IX, X, XI, XII. By inhibiting the activation of factor XIII (fibrin stabilizing factor), heparin prevents the formation of stable fibrin clots. While heparin will inhibit the reactions that lead to clotting, it does not significantly change the concentrations of clotting factors. Heparin does not lyse clots, but it can prevent the growth of existing clots.

Heparin causes increased release of lipoprotein lipase, thereby increasing the clearance of circulating lipids and boosting plasma levels of free fatty acids.

Pharmacokinetics

Heparin is not absorbed by the gut if administered orally; it must be given parenterally to be effective. Anticoagulant activity begins immediately after direct IV bolus injection, but may take up to one hour after deep SC injection. When heparin is given by continuous IV infusion, an initial bolus must be administered for full anticoagulant activity to begin.

Heparin is extensively protein bound, primarily to fibrinogen, low-density lipoproteins and globulins. It does not appreciably cross the placenta or enter milk.

Heparin's metabolic fate is not completely understood. The drug is apparently partially metabolized by the liver and also inactivated by the reticuloendothelial system. Serum half-lives in humans averages 1–2 hours.

In healthy dogs, bioavailability after subcutaneous injection is about 50%. When 200 units/kg were administered to healthy dogs SC, plasma heparin concentrations were in the therapeutic range between 1 and 6 hours after administration. (Diquelou, Barbaste et al. 2005)

Contraindications/Precautions/Warnings

Heparin is contraindicated in patients hypersensitive to it, having severe thrombocytopenia or uncontrollable bleeding (caused by something other than DIC). One author (Green 1989) states that with DIC "heparin should not be given to actively bleeding patients that have severe factor depletion and thrombocytopenia, as fatal hemorrhage may result."

Use for treating DIC has become increasingly controversial. The most recent evidence suggests that heparin should not be used during DIC in patients with concurrent inflammatory processes. Until further evidence suggests practices to the contrary, heparin should be used with extreme caution in both human and veterinary patients with dysfunctional interactions between inflammatory and hemostatic systems and the endothelium. (Bateman 2005a)

Do not administer IM as heparin may cause hematoma formation. Hematomas, pain, and irritation may occur after deep SC dosing.

Dogs with renal insufficiency may have lower plasma levels and faster elimination rates of heparin; dosage adjustment may be required.

Adverse Effects

Bleeding and thrombocytopenia are the most common adverse effects associated with heparin therapy. Because heparin is derived from bovine or porcine tissues, hypersensitivity reactions may be possible. Less commonly encountered adverse effects that have been reported in animals and/or humans include vasospastic reactions

(after several days of therapy), osteoporosis and diminished renal function (after long-term, high-dose therapy), rebound hyperlipidemia, hyperkalemia, alopecia, suppressed aldosterone synthesis and priapism. In horses, high IV dosages of heparin may cause agglutination of red cells and a decrease in hematocrits.

Reproductive/Nursing Safety

While heparin does not cross the placenta and is generally felt to be the anticoagulant of choice during pregnancy, its safe use in pregnancy has not been firmly established and pregnancy outcomes may be unfavorable. It should be used cautiously and only when clearly necessary. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Heparin is not excreted into milk.

Overdosage/Acute Toxicity

Overdosage of heparin is associated with bleeding. Clinical signs that could be seen before frank bleeding occurs include hematuria, tarry stools, petechiae, bruising, etc. Protamine can reverse heparin's effects; see the Protamine monograph for more information.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving heparin and may be of significance in veterinary patients:

- **ASPIRIN**: May increase the risk for hemorrhage
- **DEXTRAN**: May increase the risk for hemorrhage
- **NSAIDS**: May increase the risk for hemorrhage
- **WARFARIN**: May increase the risk for hemorrhage
- The following drugs may partially counteract heparin's anticoagulant effects: **ANTIHISTAMINES, NITROGLYCERIN** (IV), **PROPYLENE GLYCOL, DIGOXIN**, and **TETRACYCLINES**.

Laboratory Considerations

- Unless heparin is administered by continuous infusion, it can alter prothrombin time, (**PT**), which can be misleading in patients also receiving a coumarin or an indanedione anticoagulant.
- Heparin can interfere with the results of the **BSP** (sulfobromophthalein, bromosulfophthalein) test by changing the color intensity of the dye and shifting the absorption peak from 580 nm to 595 nm.
- Heparin can cause falsely elevated values of serum t**hyroxine** if using competitive protein binding methods of determination. Radioimmunoassay (RIA) and protein bound iodine methods are apparently unaffected by heparin.
- When heparin is used as an anticoagulant *in vitro* (*e.g.*, in **blood collection containers**), white cell counts should be performed within 2 hours of collection. Do not use heparinized blood for platelet counts, erythrocyte sedimentation rates, erythrocyte fragmentation tests, or for any tests involving complement or isoagglutinins. Errors in blood gas determinations for CO_2 pressure, bicarbonate concentration, or base excess may occur if heparin encompasses 10% or more of the blood sample.

Doses

- **DOGS & CATS:**

  For adjunctive treatment of DIC (See Contraindications/Warnings above): **Note:** Heparin therapy may be only one aspect of successful treatment of DIC. Alleviation of the precipitating causes, administration of fluids, blood, aspirin, and diligent monitoring of coagulation tests (aPTT, PT), fibrin degradation products, and fibrinogen may all be important factors in the treatment of DIC. Doses of heparin are controversial; dosage ranges and methods may vary widely depending on the clinician/author.

  a) 75 Units/kg SC three times daily (Wingfield and Van Pelt 1989)

  b) Add 5,000 U of heparin/500 mL warmed whole blood 30 minutes before transfusion. Alternatively, give 10–150 U/kg SC q12h. Heparin must be tapered over 48 hours or a "rebound effect" may occur. (Feldman 1985)

  c) After pH has been corrected and perfusion maximized, transfuse heparinized whole fresh blood or plasma (75 U/kg heparin) one time. Then begin mini-dose heparin therapy at 5–10 U/kg/hour by continuous IV infusion or 75 U/kg SC q8h. Continue without interruption until DIC has completely disappeared. With these doses, bleeding risk is negligible and aPTT monitoring not necessary, although thrombocytopenia may develop. (Slappendel 1989)

  d) Before administering heparin, provide sufficient fresh whole blood to maintain platelet counts above 30,000/microliter and fibrinogen levels over 50 mg/dl. Then give heparin at 50–100 U/kg SC q6h. Alternatively, dose heparin sufficiently to increase aPTT to 1.5–2 times normal (may be more effective in patients susceptible to thromboembolization). (Green 1989)

  For adjunctive treatment of thromboembolic disease:

  a) For feline arterial thromboembolism: 250–300 U/kg SC q8h. First dose is administered IV to cats showing signs of shock. Monitoring aPTT (1.5–2.5 fold) and ACT (15–20 sec) should be regarded as rough guidelines only, as these may still result in heparin levels below the recommended therapeutic range. (Smith 2004)

  b) Dogs: 200–500 U/kg subcutaneously every 8 hours; target aPTT to 1.5–2 times pretreatment value (Brooks 2000)

  c) For maintenance therapy for arterial thromboembolic disease in cats: 250–300 Units/kg SC every 8 hours for the initial in-hospital therapy. (Lunsford and Mackin 2007)

  d) For maintenance therapy for pulmonary thromboembolism in small animals: 200–500 Units/kg SC every 8 hours and then adjusted to reach a target aPTT of 1.5–2 times the (pre)treatment values or an anti-factor Xa activity between 0.35–0.7 U/mL. Warfarin is also given concurrently. (Lunsford and Mackin 2007)

  e) For canine arterial thrombosis and thromboembolism: Keep dog in a quiet and warm place; give analgesics if necessary. Give heparin initially at 220 U/kg IV. Correct dehydration and dilute blood by administering electrolyte solutions. Dextran products may be helpful. Follow-up doses of heparin should be started low and increased until aPTT is 2–2.5 times normal. After 3–5 days of therapy, gradually reduce heparin over 48–72 hours while dog is put on oral anticoagulant therapy (see warfarin monograph). (Suter 1989)

  To prevent clots forming when performing closed chest lavage with pyothorax:

  a) Add 1000 U of heparin per liter of lavage fluid (warm normal saline). This fluid is instilled at 20 mL/kg twice daily for 5–7 days. Antibiotics (often penicillin) or enzymes (*e.g.*, streptokinase) may also be added to fluid. (Berkwitt and Berzon 1988)

For adjunctive therapy of acute complicated or severe pancreatitis in dogs:

a) 50–75 U/kg SC twice a day to three times a day; may reduce thromboembolic tendencies, but efficacy is unknown and heparin is not indicated in all cases (Bunch 1988)

For detection of lipoprotein lipase activity (heparin stimulation test):

a) Measure serum lipids just before and 15 minutes after heparin at 100 U/kg IV. Lack of increase in lipolytic activity is suggestive of lipoprotein lipase deficiency. (Kay, Kruth, and Twedt 1988)

- **HORSES:**

For adjunctive treatment of DIC:

Note: Heparin therapy may be only one aspect of successful treatment of DIC. Alleviation of the precipitating causes, administration of fluids, blood, aspirin, and diligent monitoring of coagulation tests (APTT, PT), fibrin degradation products, and fibrinogen may all be important factors in the treatment of DIC.

a) 80–100 U/kg IV q4–6h (may be added to fluids and given as a slow drip). Low grade DIC may be treated with 25–40 U/kg SC 2–3 times a day. (Byars 1987)

As adjunctive therapy in endotoxic shock:

a) 40 Units/kg IV or SC 2–3 times a day may prevent the development of microthrombi; additional studies are required to confirm positive benefits (Semrad and Moore 1987)

As adjunctive therapy in the prevention of laminitis:

a) 25–100 Units/kg subcutaneously 3 times daily. Higher doses used when a thrombotic event is underway, lower dosages should have fewer adverse effects and still have antithrombotic activity. Ideally, APTT and ACT should be monitored. Targets are 1.5–2.5 times baseline for APTT and 1.2–1.4 times baseline for ACT. (Brumbaugh, Lopez et al. 1999)

Monitoring

Note: The frequency of monitoring is controversial and is dependent on several factors, including heparin dose, patient's condition, concomitant problems, etc. Because of the high incidence of hemorrhage associated with heparin use, frequent monitoring of aPTT is essential early in therapy (particularly using higher dosages) and in critically ill animals.

- While whole blood clotting time (WBCT), partial thromboplastin time (PTT), and activated partial thromboplastin times (aPTT) may all be used to monitor therapy, APTT is most often recommended;
- Platelet counts and hematocrit (PCV) should be done periodically;
- Occult blood in stool and urine; other observations for bleeding;
- Clinical efficacy

Client Information

- Because of the intense monitoring necessary with heparin's use and the serious nature of the disease states in which it is used, this drug should be utilized only by professionals familiar with it, preferably in an inpatient setting.

Chemistry/Synonyms

Heparin is an anionic, heterogeneous sulfated glycosaminoglycan molecule with an average molecular weight of 12,000 that is found naturally in mast cells. It is available commercially as either sodium or calcium salts and is obtained from either porcine intestinal mucosa (both calcium and sodium salts) or from bovine lung tissue (sodium salt only). Heparin sodium and calcium occur as white or pale-colored, amorphous, hygroscopic powders having a faint odor. Both are soluble in water and practically insoluble in alcohol; the commercial injections have a pH of 5–7.5. Heparin potency is expressed in terms of USP Heparin units and values are obtained by comparing against a standard reference from the USP. The USP requires that potencies be not less than 120 units/mg on a dried basis for heparin derived from lung tissue, and 140 units/mg when derived from all other tissue sources.

Heparin sodium may also be as: heparinum natricum, sodium heparin, and soluble heparin; many trade names are available.

Storage/Stability/Compatibility

Heparin solutions should be stored at room temperature (15–30°C) and not frozen. Avoid excessive exposure to heat.

Heparin sodium is reportedly physically **compatible** with the following intravenous solutions and drugs: amino acids 4.25%-dextrose 25%, dextrose-Ringer's combinations, dextrose-lactated Ringer's solutions, fat emulsion 10%, Ringer's injection, Normosol R, aminophylline, amphotericin B with or without hydrocortisone sodium phosphate, ascorbic acid injection, bleomycin sulfate, calcium gluconate, cephapirin sodium, chloramphenicol sodium succinate, clindamycin phosphate, dimenhydrinate, dopamine HCl, erythromycin gluceptate, isoproterenol HCl, lidocaine HCl, methylprednisolone sodium succinate, metronidazole with sodium succinate, nafcillin sodium, norepinephrine bitartrate, potassium chloride, prednisolone sodium succinate, promazine HCl, sodium bicarbonate, verapamil HCl, and vitamin B-complex with or without vitamin C.

Heparin **compatibility information conflicts** or is dependent on diluent or concentration factors with the following drugs or solutions: dextrose-saline combinations, dextrose in water, lactated Ringer's injection, saline solutions, ampicillin sodium, cephalothin sodium, dobutamine HCl, hydrocortisone sodium succinate, methicillin sodium, oxytetracycline HCl, penicillin G sodium/potassium, and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Heparin sodium is reported physically **incompatible** when mixed with the following solutions or drugs: sodium lactate 1/6 M, amikacin sulfate, chlorpromazine HCl, codeine phosphate, cytarabine, daunorubicin HCl, diazepam, doxorubicin HCl, droperidol HCl with and without fentanyl citrate, erythromycin lactobionate, gentamicin sulfate, hyaluronidase, kanamycin sulfate, levorphanol bitartrate, meperidine HCl, methadone HCl, morphine sulfate, pentazocine lactate, phenytoin sodium, polymyxin B sulfate, streptomycin sulfate, and vancomycin HCl.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Heparin Sodium Injection: 1000 U/mL, 2000 U/mL, 2500 U/mL, 5000 U/mL, 10,000 U/mL, 20,000 U/mL, & 40,000 U/mL in 0.5, 1, 2, 4, 5, 10, and 30 mL amps, vials and multi-dose vials (depending on concentration and manufacturer); generic; (Rx).

Heparin Unit-Dose Sodium Injection: 1000 U/dose, 2500 U/dose, 5000 U/dose, 7500 U/dose, 10,000 U/dose and 20,000 U/dose in 1, 10, and 30 mL *Dosette* vials, 0.5 mL & 1 mL *Tubex*, 0.5, 1, 4 and 10 mL vials, and 1 mL fill in 2 mL *Carpuject* (depending on concentration and manufacturer); generic; (Rx)

Heparin Sodium and 0.9% Sodium Chloride Injection: 1000 and 2000 units in 500 mL and 1000 mL, respectively; in *Viaflex* (Baxter Healthcare); (Rx)

Heparin Sodium and 0.45% Sodium Chloride Injection: 12,500 and 25,000 units in 250 mL (12,500 only) and 500 mL; (Abbott); (Rx)

Heparin Sodium Lock Flush Solution— (IV use) Injection: 1 unit/mL in 1, 2, 2.5, 5 & 10 mL syringes; 10 U/mL and 100 U/mL in 1, 2, 5, 10 mL (regular and preservative free), 30 mL and 50 mL vials; 1 (regular and preservative free) and 2 mL *Dosette* vials; 1, 2.5 mL *Dosette* cartridge needle units; 1 mL amps; 1, 2, 2.5, 3, and 5 mL disposable syringes; *Hep-Lock®* and *Hep-Loc® U/P* (Elkins-Sinn); *Hepflush-10®* (American Pharmaceutical Partners); *Heparin I.V. Flush* (Medefil); generic; (Rx)

HETASTARCH

(***het***-a-starch)

COLLOID VOLUME EXPANDER

Prescriber Highlights

- Volume expander used to treat hypovolemia where colloidal therapy required
- Contraindications: Severe heart failure, severe bleeding disorders, & patients in oliguric or anuric renal failure
- Caution: Thrombocytopenia, patients undergoing CNS surgery; liver disease
- May cause volume overload: Use with caution in patients with renal dysfunction, congestive heart failure, or pulmonary edema
- Adverse Effects: Coagulopathies possible; too rapid administration to small animals (especially cats) may cause nausea/vomiting; hypersensitivity reactions possible but very rare

Uses/Indications

In hypovolemic patients where total protein is less than 3.5 g/dl and crystalloid therapy is likely to reduce this level further, colloid therapy (plasma, dextran or hetastarch) should be considered as part of intravascular volume restoration. It is often used when colloid therapy is required and blood products are unavailable, or time is of the essence and the wait for crossmatching is unacceptable. Because of the expense, hetastarch is generally used only in small animals.

Pharmacology/Actions

Hetastarch acts as a plasma volume expander by increasing the oncotic pressure within the intravascular space similarly to either dextran or albumin. Maximum volume expansion occurs within a few minutes of the completion of infusion. Duration of effect is variable, but may persist for 24 hours or more. When added to whole blood in humans, hetastarch causes an increase in erythrocyte sedimentation rate.

Pharmacokinetics

Lower molecular weight molecules, (less than 50,000) are rapidly excreted by the kidneys; larger molecules are slowly degraded enzymatically to a size where they then can be excreted. About 40% of a dose is excreted in the first 24 hours after infusion. After about 2 weeks, practically all of the drug is excreted.

Contraindications/Precautions/Warnings

In humans, hetastarch is contraindicated in patients with severe heart failure, severe bleeding disorders and patients in oliguric or anuric renal failure.

It is believed that significant bleeding can occur if hetastarch is used in animals with compromised coagulation systems. For example, use in patients with von Willebrand's disease could significantly increase the risk for bleeding.

Because of the danger of volume overload, use of hetastarch for the treatment of shock not accompanied by hypovolemia may be hazardous. As it has no oxygen carrying capacity, hetastarch is not a replacement for whole blood or red blood cells.

Because of its effect on platelets, hetastarch should be used with caution in patients with thrombocytopenia and with extreme caution in patients undergoing CNS surgery. Because of its effects on indirect serum bilirubin levels, hetastarch should be used with caution in patients with liver disease.

Because of the threat of volume overload, hetastarch should be used in caution in patients with renal dysfunction, congestive heart failure or pulmonary edema.

Adverse Effects

Hetastarch can affect platelet function and clotting tests can be transiently prolonged. It is less antigenic than dextran, but can cause sensitivity reactions and interfere with antigen-antibody testing. Anaphylactic reactions and coagulopathies are considered to occur rarely, however.

When given via rapid infusion to cats, hetastarch may cause signs of nausea and vomiting; if administered over 15–30 minutes, these signs are eliminated. At recommended dosages, hetastarch may cause minor changes in clotting times and platelet counts due to direct (precipitation of factor VIII) and dilutional causes. Clinically these effects are usually insignificant, but patients with preexisting coagulopathies may be predisposed to further bleeding.

In humans, increases in serum indirect bilirubin have occurred occasionally. No effect on other liver function tests were noted and the increases subsided over several days. Serum amylase levels may be falsely elevated for several days after hetastarch is administered. While clinically insignificant, the changes may preclude using serum amylase to diagnosis or monitor patients with acute pancreatitis.

Circulatory overload leading to pulmonary edema is possible, particularly when large dosages are administered to patients with diminished renal function. Do not give intramuscularly as bleeding, bruising, or hematomas may occur.

Reproductive/Nursing Safety

Hetastarch's safety during pregnancy has not been established, but no untoward effects have apparently been reported. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

It is not known whether hetastarch is excreted in milk, but it is unlikely to pose much risk to offspring.

Overdosage/Acute Toxicity

Overdosage could result in volume overload in susceptible patients. Dose and monitor fluid status carefully.

Drug Interactions

Hetastarch apparently has no drug interactions that are clinically significant.