FRESENIUS KABI

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HEPARIN LOCK FLUSH
SOLUTION, USP

Rx only

HEPARIN LOCK FLUSH SOLUTION IS INTENDED FOR MAINTENANCE OF PATENCY OF INTRAVENOUS INJECTION DEVICES ONLY AND IS NOT TO BE USED FOR ANTICOAGULANT THERAPY.

DERIVED FROM PORCINE INTESTINAL MUCOSA.

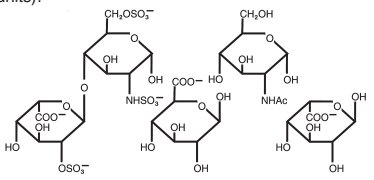
Available as: Preservative Free **or** Contains Parabens.

DESCRIPTION:

Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, having anticoagulant properties. Although others may be present, the main sugars occurring in heparin are: (1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2) > (1) > (4) > (3) > (5), and are joined by glycosidic linkages, forming polymers of varying sizes. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions.

Heparin Lock Flush Solution, USP is a sterile preparation of heparin sodium derived from porcine intestinal mucosa, standardized for anticoagulant activity, with sufficient sodium chloride to make it isotonic with blood. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

Structure of Heparin Sodium (representative subunits):



(1) (2) (3) (4) (5)

Heparin Lock Flush Solution, USP (porcine), preservative free, is available as follows:

Each mL contains: 10 USP Units Heparin sodium (porcine); 9 mg sodium chloride; Water for Injection q.s. Sodium hydroxide and/or hydrochloric acid for pH adjustment (5.0 to 7.5).

Each mL contains: 100 USP Units Heparin sodium (porcine); 9 mg sodium chloride; Water for Injection q.s. Sodium hydroxide and/or hydrochloric acid for pH adjustment (5.0 to 7.5).

Heparin Lock Flush Solution, USP (porcine), preserved with parabens, is available as follows:

Each mL contains: 10 or 100 USP Units Heparin sodium (porcine); 9 mg sodium chloride; 0.15% methylparaben and 0.015% propylparaben added as preservatives; Water for Injection q.s. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment (5.0 to 7.5).

CLINICAL PHARMACOLOGY:
Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases, it is not measurably affected by low doses of heparin. Loglinear plots of heparin plasma concentrations with time, for a wide range of dose levels, are linear, which suggests the absence of zero order processes. Liver and the reticulo-endothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2}$ = 10 minutes) and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.

Patients over 60 years of age, following similar doses of heparin, may have higher plasma levels of heparin and longer activated partial thromboplastin times (APTTs) compared with patients under 60 years of age.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

INDICATIONS AND USAGE:
Heparin Lock Flush Solution, is intended to maintain patency of an indwelling venipuncture device designed for intermittent injection or infusion therapy or blood sampling. Heparin Lock Flush Solution, may be used following initial placement of the device in the vein, after each injection of a medication or after withdrawal of blood for laboratory tests (see **DOSAGE AND ADMINISTRATION, *Maintenance of Patency of IV Devices,*** for direction for use).

Heparin Lock Flush Solution, USP is not to be used for anticoagulant therapy.

CONTRAINDICATIONS:
Heparin sodium should NOT be used in patients with the following conditions: severe thrombocytopenia; an uncontrollable active bleeding state (see **WARNINGS**), except when this is due to disseminated intravascular coagulation.

WARNINGS:
Heparin is not intended for intramuscular use.

Hypersensitivity
Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations (see **ADVERSE REACTIONS, *Hypersensitivity***).

Hemorrhage
Hemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure or any other unexplained symptom should lead to serious consideration of a hemorrhagic event.

Heparin sodium should be used with extreme caution in infants and in patients with disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exists are:

Cardiovascular—Subacute bacterial endocarditis, severe hypertension.

Surgical—During and immediately following (a) spinal tap or spinal anesthesia or (b) major surgery, especially involving the brain, spinal cord or eye.

Hematologic—Conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia and some vascular purpuras.

Gastrointestinal—Ulcerative lesions and continuous tube drainage of the stomach or small intestine.

Other—Menstruation, liver disease with impaired hemostasis.

Thrombocytopenia
Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. Platelet counts should be obtained at baseline and periodically during heparin administration. Mild thrombocytopenia (count greater than 100,000/mm^3) may remain stable or reverse even if heparin is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100,000/mm^3 or if recurrent thrombosis develops (see ***Heparin-induced Thrombocytopenia and Heparin-induced Thrombocytopenia and Thrombosis***), the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered.

Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT)
Heparin-induced Thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as Heparin-induced Thrombocytopenia and Thrombosis (HITT). Thrombotic events may also be the initial presentation for HITT. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischemia, stroke, myocardial infarction, mesenteric thrombosis, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, and possibly death. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3 or if recurrent thrombosis develops, the heparin product should be promptly discontinued and alternative anticoagulants considered if patients require continued anticoagulation.

Delayed Onset of HIT and HITT
Heparin-induced Thrombocytopenia and Heparin-induced Thrombocytopenia and Thrombosis can occur up to several weeks after the discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for HIT and HITT.

Use in Neonates and Infants
Preservative-Free Heparin Lock Flush Solution, USP should be used for maintaining the patency of intravenous injection devices in neonates.

The 100 unit/mL concentration should not be used in neonates or in infants who weigh less than 10 kg because of the risk of systemic anticoagulation. Caution is necessary when using the 10 unit/mL concentration in premature infants who weigh less than 1 kg who are receiving frequent flushes since a therapeutic heparin dose may be given to the infant in a 24-hour period.

PRECAUTIONS:
General
In infants, the cumulative amounts of heparin received from the frequent administration of Heparin Lock Flush Solution during a 24-hour period must be considered.

Precautions must be exercised when drugs which are incompatible with heparin are administered through an indwelling intravenous catheter containing Heparin Lock Flush Solution (see **DOSAGE AND ADMINISTRATION, *Maintenance of Patency of IV Devices***).

Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT)
See **WARNINGS**.

Increased Risk to Older Patients, Especially Women—A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.

Laboratory Tests
Periodic platelet counts, hematocrits and tests for occult blood in stool are recommended during the entire course of heparin use (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions
Platelet Inhibitors—Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

Other Interactions—Digitalis, tetracyclines, nicotine or antihistamines may partially counteract the anticoagulant action of heparin sodium.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed to evaluate the carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

Pregnancy
Teratogenic Effects: Pregnancy Category C
Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects
Heparin does not cross the placental barrier.

Nursing Mothers
Heparin is not excreted in human milk.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Not for use in neonates (see **WARNINGS, *Use in Neonates and Infants***).

Preservative-Free Heparin Lock Flush Solution, USP should be used for maintaining the patency of intravenous injection devices in neonates (see **WARNINGS**).

Geriatric Use
A higher incidence of bleeding has been reported in patients over 60 years of age, especially women (see **PRECAUTIONS, *General*** and **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS:
Hemorrhage
Hemorrhage is the chief complication that may result from heparin use (see **WARNINGS, *Hemorrhage***). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see **OVERDOSAGE**).

Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT) and Delayed Onset of HIT and HITT
See **WARNINGS**.

Local Irritation
Local irritation and erythema have been reported with the use of Heparin Lock Flush Solution.

Hypersensitivity
Generalized hypersensitivity reactions have been reported, with chills, fever and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar side of the feet, may occur.

Thrombocytopenia has been reported to occur in patients receiving heparin, with a reported incidence of 0 to 30%. While often mild and of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death (see **WARNINGS** and **PRECAUTIONS**).

Certain episodes of painful, ischemic and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are in fact identical to the thrombocytopenia-associated complications remains to be determined.

OVERDOSAGE:

Symptoms

Bleeding is the chief sign of heparin overdosage. Nosebleeds, blood in urine or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

Treatment*—Neutralization of Heparin Effect*

When clinical circumstances (bleeding) require reversal of heparinization, protamine sulfate (1% solution) by slow infusion will neutralize heparin sodium. ***No more than 50 mg*** should be administered, ***very slowly,*** in any 10 minute period. Each mg of protamine sulfate neutralizes approximately 100 USP heparin units. The amount of protamine required decreases over time as heparin is metabolized. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about 1/2 hour after intravenous injection.

Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions often resembling anaphylaxis have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For additional information consult the labeling of Protamine Sulfate Injection, USP products.

DOSAGE AND ADMINISTRATION:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight discoloration does not alter potency.

Preservative-Free Heparin Lock Flush Solution, USP should be used for maintaining the patency of intravenous injection devices in neonates (see **WARNINGS**).

Heparin Lock Flush Solution, USP in the 100 unit/mL concentration is **not recommended for use in neonates and infants** (see **WARNINGS, *Use in Neonates and Infants***).

Maintenance of Patency of IV Devices

To prevent clot formation in a heparin lock set or central venous catheter following its proper insertion, Heparin Lock Flush Solution, USP is injected via the injection hub in a quantity sufficient to fill the entire device. This solution should be replaced each time the device is used. Aspirate before administering any solution via the device in order to confirm patency and location of needle or catheter tip. If the drug to be administered is incompatible with heparin, the entire device should be flushed with normal saline before and after the medication is administered; following the second saline flush, the Heparin Lock Flush Solution, USP may be reinstilled into the device. The device manufacturer's instructions should be consulted for specifics concerning its use. Usually this dilute heparin solution will maintain anticoagulation within the device for up to 4 hours.

NOTE: Since repeated injections of small doses of heparin can alter tests for activated partial thromboplastin time (APTT), a baseline value for APTT should be obtained prior to insertion of an intravenous device.

Withdrawal of Blood Samples

Heparin Lock Flush Solution, USP may also be used after each withdrawal of blood for laboratory tests. When heparin would interfere with or alter the results of blood tests, the heparin solution should be cleared from the device by aspirating and discarding it before withdrawing the blood sample.

HOW SUPPLIED:
Heparin Lock Flush Solution, USP (porcine), **preservative free,** is available in packages of 25, as follows:

Product No.	NDC No.	Strength	Fill Volume
504901	63323-549-01	100 USP units per 1 mL	1 mL fill in a 3 mL flip-top, single dose plastic vial.
505701	63323-557-01	10 USP units per 1 mL	1 mL fill in a 3 mL flip-top, single dose plastic vial.

Unused portion of the vial should be discarded. Use only if solution is clear and seal intact.

This container closure is not made with natural rubber latex.

Heparin Lock Flush Solution, USP (porcine), contains **parabens**, and is available in multiple dose vials, in packages of 25, as follows:

Product No.	NDC No.	Strength	Fill Volume
504401*	63323-544-01	10 USP units per 1 mL	1 mL fill in a 3 mL vial.
504411	63323-544-11	100 USP units per 10 mL (10 USP units per mL)	10 mL fill in a 10 mL vial.
504501*	63323-545-01	100 USP units per 1 mL	1 mL fill in a 3 mL vial.
504505	63323-545-05	500 USP units per 5 mL (100 USP units per mL)	5 mL fill in a 6 mL vial.

*Packaged in a plastic vial.

Do not use if solution is discolored or contains a precipitate.

This container closure is not made with natural rubber latex.

STORAGE:
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

REFERENCES:

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3. Rice L, Attisha W, Drexler A, Francis J. Delayed-Onset Heparin Induced Thrombocytopenia. *Annals of Internal Medicine*, 2002;136:210-215.
4. Dieck J., C. Rizo-Patron, et al. (1990). "A New Manifestation and Treatment Alternative for Heparin-Induced Thrombosis." Chest 98(1524-26).
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6. Divgi A. (Reprint), Thumma S., Hari P., Friedman K., Delayed Onset Heparin-Induced Thrombocytopenia (HIT) Presenting After Undocumented Drug Exposure as Post-Angiography Pulmonary Embolism. *Blood*. 2003;102(11):127b.

FRESENIUS KABI
Fresenius Kabi USA, LLC
Lake Zurich, IL 60047

For Product Inquiry: 1-800-551-7176

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