

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HEPARIN SODIUM IN SODIUM CHLORIDE INJECTION safely and effectively. See full prescribing information for HEPARIN SODIUM IN SODIUM CHLORIDE INJECTION.

HEPARIN SODIUM IN SODIUM CHLORIDE injection, for intravenous use

Initial U.S. Approval: 1939

INDICATIONS AND USAGE

Heparin Sodium in Sodium Chloride Injection at a concentration of 2 units/mL is indicated as an anticoagulant to maintain catheter patency. (1)

DOSAGE AND ADMINISTRATION

Infuse through intravenous catheter at a rate of 6 units per hour. (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 1,000 USP units in Sodium Chloride in 500 mL single-dose infusion bag (2 USP units per mL) (3)
- Injection: 2,000 USP units in Sodium Chloride per 1,000 mL single-dose infusion bag (2 USP units per mL) (3)

CONTRAINDICATIONS

Heparin Sodium in Sodium Chloride Injection is contraindicated in patients with the following conditions: (4)

- With an uncontrollable active bleeding state, except when this is due to disseminated intravascular coagulation (5.1)
- With a history of heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis (HITT) (5.2)

- With severe thrombocytopenia (5.2, 5.3)
- Known hypersensitivity to heparin or pork products (5.5)

WARNINGS AND PRECAUTIONS

- **Hemorrhage:** Fatal cases have occurred. Monitor for signs of bleeding and manage promptly. (5.1)
- **HIT and HITT:** Monitor for signs and symptoms and discontinue if indicative of HIT or HITT. (5.2)

ADVERSE REACTIONS

Most common adverse reactions are: hemorrhage, thrombocytopenia, HIT and HITT, hypersensitivity, and elevations of aminotransferase levels. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drugs that interfere with platelet aggregation or drugs that counteract coagulation may induce bleeding (7.2)

USE IN SPECIFIC POPULATIONS

Geriatric Use: A higher incidence of bleeding has been reported in patients over 60 years of age, especially women (5.7, 8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Heparin Sodium in Sodium Chloride Injection at a concentration of 2 units/mL is indicated as an anticoagulant to maintain catheter patency.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Do not administer unless solution is clear and seal is intact. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Use of a final filter is recommended during administration of all parenteral solutions, where possible.

Warning: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

To Open:

Tear overwrap down side at slit and remove solution container. Visually inspect the container. If the outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found discard solution as sterility may be impaired. Do not add supplementary medication.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

All injections in VIAFLEX PLUS plastic containers are intended for administration using sterile equipment.

Because dosages of this drug are titrated to response, **no additives should be made to Heparin Sodium in Sodium Chloride Injection.**

Heparin sodium is not effective by oral administration and Heparin Sodium in Sodium Chloride Injection should not be given orally.

2.2 Maintenance of Catheter Patency

The recommended starting dose is 6 units per hour by intravenous infusion through an intravenous catheter to maintain catheter patency.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 1,000 USP units per 500 mL (2 units per mL) clear solution in a single-dose infusion bag
- Injection: 2,000 USP units per 1,000 mL (2 units per mL) clear solution in a single-dose infusion bag

4 CONTRAINDICATIONS

The use of Heparin Sodium in Sodium Chloride Injection is contraindicated in patients with the following conditions:

- Uncontrollable active bleeding state, except when this is due to disseminated intravascular coagulation [*see Warnings and Precautions (5.1)*]
- History of heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia with thrombosis (HITT) [*see Warnings and Precautions (5.2)*];
- Severe thrombocytopenia [*see Warnings and Precautions (5.2, 5.3)*].
- Known hypersensitivity to heparin or pork products (e.g., anaphylactoid reactions) [*see Adverse Reactions (6.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Avoid using heparin in the presence of major bleeding, except when the benefits of heparin therapy outweigh the potential risks.

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

Use heparin sodium with caution in disease states in which there is increased risk of hemorrhage, including:

- 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.
- Patients with hereditary antithrombin III deficiency receiving concurrent antithrombin III therapy – The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. To reduce the risk of bleeding, reduce the heparin dose during concomitant treatment with antithrombin III (human).
- Other - Menstruation, liver disease with impaired hemostasis.

5.2 Heparin-Induced Thrombocytopenia and Heparin-Induced Thrombocytopenia with Thrombosis

Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated reaction. HIT occurs in patients treated with heparin and is due to the development of antibodies to a platelet Factor 4-heparin complex that induce *in vivo* platelet aggregation. HIT may progress to the development of venous and arterial thromboses, a condition referred to as heparin-induced thrombocytopenia with 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.

If the platelet count falls below $100,000/\text{mm}^3$ or if recurrent thrombosis develops, promptly discontinue heparin, evaluate for HIT and HITT, and, if necessary, administer an alternative anticoagulant. HIT or HITT can occur up to several weeks after the discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin sodium should be evaluated for HIT or HITT.

5.3 Thrombocytopenia

Thrombocytopenia in patients receiving heparin has been reported at frequencies up to 30%. It can occur 2 to 20 days (average 5 to 9) following the onset of heparin therapy. Obtain platelet counts before and periodically during heparin therapy. If the count falls below 100,000/mm³ or if recurrent thrombosis develops, promptly discontinue heparin, evaluate for HIT and HITT, and, if necessary, administer an alternative anticoagulant [*see Warnings and Precautions (5.2)*].

5.4 Heparin Resistance

Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

5.5 Hypersensitivity

Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations. Because Heparin Sodium in Sodium Chloride Injection is derived from animal tissue, it should be used with caution in patients with a history of allergy to pork products.

5.6 Hypokalemia

Excessive administration of potassium free solutions may result in significant hypokalemia.

5.7 Increased Risk of Bleeding in Older Patients, Especially Women

A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age [*see Use in Specific Populations (8.5)*].

5.8 Laboratory Tests

Periodic platelet counts, hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hemorrhage [*see Warnings and Precautions (5.1)*].
- Heparin-Induced Thrombocytopenia and Heparin-Induced Thrombocytopenia with Thrombosis [*see Warnings and Precautions (5.2)*]

- Thrombocytopenia [*see Warnings and Precautions (5.3)*]
- Heparin Resistance [*see Warnings and Precautions (5.4)*]
- Hypersensitivity [*see Warnings and Precautions (5.5)*]

6.1 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of heparin sodium. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Hemorrhage

Hemorrhage is the chief complication that may result from heparin therapy [*see Warnings and Precautions (5.1)*]. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug [*see Overdosage (10)*]. Gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. Bleeding can occur at any site but certain specific hemorrhagic complications may be difficult to detect:

- Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy, including fatal cases.
- Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short or long-term anticoagulant therapy.
- Retroperitoneal hemorrhage

HIT and HITT, including delayed onset cases [*see Warnings and Precautions (5.2, 5.3)*].

Histamine-like reactions: Such reactions have been observed at the site of injections. Necrosis of the skin has been reported at the site of subcutaneous injection of heparin, occasionally requiring skin grafting.

Hypersensitivity: General 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 site of the feet, may occur [*see Warnings and Precautions (5.5)*].

Elevations of serum aminotransferases: Significant elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have occurred in patients who have received heparin.

Others: Cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipemia on discontinuation of heparin sodium have also been reported.

7 DRUG INTERACTIONS

7.1 Oral Anticoagulants

Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose or 24 hours after the last subcutaneous dose should elapse before blood is drawn if a valid prothrombin time is to be obtained.

7.2 Platelet Inhibitors

Drugs such as NSAIDs (including acetylsalicylic acid, ibuprofen, indomethacin, and celecoxib), dextran, phenylbutazone, thienopyridines, dipyridamole, hydroxychloroquine, glycoprotein IIb/IIIa antagonists (including abciximab, eptifibatid, and tirofiban), 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. To reduce the risk of bleeding, a reduction in the dose of antiplatelet agent or heparin is recommended.

7.3 Other Medications that May Interfere with Heparin

Digitalis, tetracyclines, nicotine or antihistamines may partially counteract the anticoagulant action of heparin sodium. Intravenous nitroglycerin administered to heparinized patients may result in a decrease of the partial thromboplastin time with subsequent rebound effect upon discontinuation of nitroglycerin. Careful monitoring of partial thromboplastin time and adjustment of heparin dosage are recommended during coadministration of heparin and intravenous nitroglycerin.

Antithrombin III (human) – The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. To reduce the risk of bleeding, a reduced dosage of heparin is recommended during treatment with antithrombin III (human).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Heparin Sodium in Sodium Chloride Injection use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In published reports heparin exposure during pregnancy did not show evidence of an increased risk of adverse maternal or fetal outcomes in humans (*see Data*). Consider the benefits and risks of Heparin Sodium in Sodium Chloride Injection for the mother and possible risks to the fetus when prescribing Heparin Sodium in Sodium Chloride Injection to a pregnant woman.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Human Data

The maternal and fetal outcomes associated with uses of heparin via various dosing methods and administration routes during pregnancy have been investigated in numerous studies. These studies generally reported normal deliveries with no maternal or fetal bleeding and no other complications.

Animal Data

In a published study conducted in rats and rabbits, pregnant animals received heparin intravenously during organogenesis at a dose of 10,000 units/kg/day, more than 50 times the maximum human daily dose based on body weight. The number of early resorptions increased in both species. There was no evidence of teratogenic effects.

8.2 Lactation

Risk Summary

There is no information regarding the presence of heparin in human milk, the effects on the breastfed child, or the effects on milk production. Due to its large molecular weight, heparin is not likely to be excreted in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for heparin and any potential adverse effects on the breastfed child from heparin or from the underlying maternal condition.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.4 Geriatric Use

A higher incidence of bleeding has been reported in patients over 60 years of age, especially women [*see Warnings and Precautions (5.7)*]. Clinical studies indicate that lower doses of heparin may be indicated in these patients [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Bleeding is the chief sign of heparin overdosage.

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 30 minutes after intravenous injection.

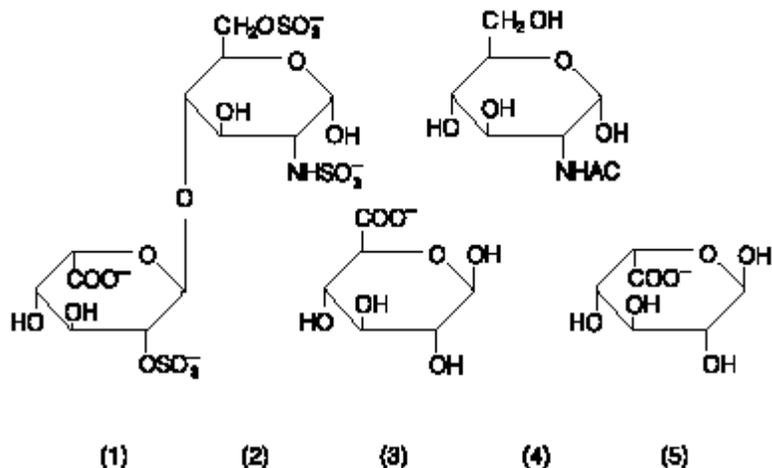
Because fatal reactions often resembling anaphylaxis have been reported with protamine, it should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For additional information consult the labeling of Protamine Sulfate Injection.

11 DESCRIPTION

Heparin is a heterogenous 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 Sodium in Sodium Chloride Injection is a buffered, sterile, nonpyrogenic solution of Heparin Sodium, USP derived from porcine intestinal mucosa, standardized for anticoagulant activity supplied in single dose containers for vascular administration. It contains no antimicrobial agents. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram. Composition, osmolarity, pH and ionic concentration are shown in Table 1.

Table 1. Composition, Osmolarity, pH, and Ionic Concentration of Heparin in 0.9% Sodium Chloride Injection

	Size (mL)	Composition					*Osmolarity (mOsmol/L) (actual)	pH	Ionic Concentration (mEq/L)			
		Heparin Sodium, USP (units/mL)	Sodium Chloride, USP (NaCl) (g/L)	Dibasic Sodium Phosphate Heptahydrate, USP (Na ₂ HPO ₄ •7H ₂ O) (g/L)	Dibasic Sodium Phosphate Dodecahydrate, USP (Na ₂ HPO ₄ •12H ₂ O) (g/L)	Citric Acid Hydrous, USP (C ₆ H ₈ O ₇ •H ₂ O) (g/L)			Sodium	Chloride	Phosphate (as HPO ₄ ⁻)	Citrate
1000 USP Heparin Units in 0.9% Sodium Chloride Injection 0338-0431-03 (Jayuya, PR)	500	2	9	4.34	-----	0.4	322	7.0 (6.0 to 8.0)	186	154	32 (16 mmol/L)	6
1000 USP Heparin Units in 0.9% Sodium Chloride Injection 0338-0424-18 (Toongabbie, AUS)	500	2	9	-----	5.80	0.4	322	7.0 (6.0 to 8.0)	186	154	32 (16 mmol/L)	6
2000 USP Heparin Units in 0.9% Sodium Chloride Injection 0338-0433-04 (Jayuya, PR)	1000	2	9	4.34	-----	0.4	322	7.0 (6.0 to 8.0)	186	154	32 (16 mmol/L)	6

* Normal physiologic osmolarity range is approximately 280 to 310 mOsmol/L.
Administration of substantially hypertonic solutions (≥ 600 mOsmol/L) may cause vein damage.

This VIAFLEX PLUS plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 Plastic). VIAFLEX PLUS on the container indicates the

presence of a drug additive in a drug vehicle. The VIAFLEX PLUS plastic container system utilizes the same container as the VIAFLEX plastic container system. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, *e.g.*, di-2- ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Heparin interacts with the naturally occurring plasma protein, Antithrombin III, to induce a conformational change, which markedly enhances the serine protease activity of Antithrombin III, thereby inhibiting the activated coagulation factors involved in the closing sequence, particularly Xa and IIa. Small amounts of heparin inhibit Factor Xa, and larger amounts inhibit thrombin (Factor IIa). Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor. Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

12.2 Pharmacodynamics

Various times (activated clotting time, activated partial thromboplastin time, prothrombin time, whole blood clotting time) are prolonged by full therapeutic doses of heparin; in most cases, they are not measurably affected by low doses of heparin. Bleeding time is usually unaffected by heparin.

12.3 Pharmacokinetics

Absorption

Heparin is not absorbed through the gastrointestinal tract and therefore administered via parenteral route. Peak plasma concentration and the onset of action are achieved immediately after intravenous administration.

Distribution

Heparin is highly bound to antithrombin, fibrinogens, globulins, serum proteases and lipoproteins. The volume of distribution is 0.07 L/kg.

Elimination

Metabolism

Heparin does not undergo enzymatic degradation.

Excretion

Heparin is mainly cleared from the circulation by liver and reticuloendothelial cells mediated uptake into extravascular space. Heparin undergoes biphasic clearance, a) rapid saturable clearance (zero order process due to binding to proteins, endothelial cells and macrophage) and b) slower first order elimination. The plasma half-life is dose-dependent, and it ranges from 0.5 to 2 h.

Specific Populations

Geriatric Patients

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 [see *Use in Specific Populations (8.5)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Heparin Sodium in Sodium Chloride Injection in VIAFLEX PLUS plastic container is supplied as follows:

Product Description	Size	Code	NDC
1,000 USP Heparin Units in Sodium Chloride Injection	500 mL	2B0953	0338-0431-03
1,000 USP Heparin Units in Sodium Chloride Injection	500 mL	AHB0953U	0338-0424-18
2,000 USP Heparin Units in Sodium Chloride Injection	1,000 mL	2B0944	0338-0433-04

Store at 25°C (77°F). Brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat.

17 PATIENT COUNSELING INFORMATION

Hemorrhage

Inform patients that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they are treated with heparin, and that they should report any unusual bleeding or bruising to their physician. Hemorrhage can occur at virtually any site in patients receiving heparin. Fatal hemorrhages have occurred [*see Warnings and Precautions (5.1)*].

Prior to Surgery

Advise patients to inform physicians and dentists that they are receiving heparin before any surgery is scheduled [*see Warnings and Precautions (5.1)*].

Heparin-Induced Thrombocytopenia

Inform patients of the risk of heparin-induced thrombocytopenia (HIT). HIT may progress to the development of venous and arterial thromboses, a condition known as heparin-induced thrombocytopenia with thrombosis (HITT). HIT and HITT can occur up to several weeks after the discontinuation of heparin therapy [*see Warnings and Precautions (5.2)*].

Hypersensitivity

Inform patients that generalized hypersensitivity reactions have been reported. Necrosis of the skin has been reported at the site of subcutaneous injection of heparin [*see Warnings and Precautions (5.5), Adverse Reactions (6.1)*].

Other Medications

Because of the risk of hemorrhage, advise patients to inform their physicians and dentists of all medications they are taking, including non-prescription medications, and before starting any new medication [*see Drug Interactions (7.3)*].

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