Important Prescribing Information

October 31, 2017

Subject: Temporary importation of intravenous drug products to address drug shortages

Dear Healthcare Professional,

In order to address shortages of critical drug products from the aftermath of Hurricane Maria, Baxter Healthcare Corporation (Baxter) is coordinating with the U.S. Food and Drug Administration (FDA) to increase the availability of products from Baxter's manufacturing facility in the United Kingdom (UK).

Baxter has initiated temporary importation of Heparin Sodium 2,000 IU/L in 0.9% w/v Sodium Chloride IV Infusions in VIAFLEX Container. This product is manufactured by Baxter's manufacturing facility in the UK and marketed in the UK. At this time, no other entity except Baxter is authorized by the FDA to import or distribute these products in the United States. FDA has not approved Heparin Sodium BP in 0.9% w/v Sodium Chloride IV Infusions in VIAFLEX container manufactured by Baxter's manufacturing facility in the UK.

Effective immediately, and during this temporary period, Baxter will offer the following:

Product name and description	**Size**	**Product code**	**Pack Factor**	**NDC**
Heparin Sodium BP 2,000 IU/L in 0.9% w/v Sodium Chloride IV Infusion in VIAFLEX container **(1,000 units / 500 mL)**	500 mL	FKB0953G	20	0338-9556-20
Heparin Sodium BP 2,000 IU/L in 0.9% w/v Sodium Chloride IV Infusion in VIAFLEX container **(2,000 units / 1,000 mL)**	1,000 mL	FKB0944G	10	0338-9552-10

BP = British Pharmacopoeia

It is important to note the following:

- The imported products are labeled in IU/L, whereas the FDA-approved heparin products are labeled in units per mL. The imported products and FDA-approved products contain the same Heparin Sodium concentration of 2 units per mL.
- The administration port protector on the imported products contains a twist-off port protector that must be twisted off rather than pulled off. The FDA approved product includes a medication (injection) port while the imported products do not include such a port. Please refer to the image below and the product comparison chart at the end of this letter.

- The imported product's administration port system is fully compatible with IV set spike heads that meet the International Organization of Standardization (ISO) standards and with Baxter IV sets marketed in the United States.

- **The barcode may not register accurately on the U.S. scanning systems.** Institutions should manually input the product into their systems to confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

There are some key differences in the labeling between the U.S. marketed Heparin Sodium and 0.9% Sodium Chloride Injection and the UK products. Please see the product comparison table at the end of this letter.

Please refer to the FDA-approved package insert for the full prescribing information of Heparin Sodium and 0.9% Sodium Chloride Injection drug product at:
https://www.dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=0d929726-76c3-48fc-b4e7-fd06409f9fb3&type=pdf&name=0d929726-76c3-48fc-b4e7-fd06409f9fb3

If you have any questions about the information contained in this letter or the use of the imported products, please contact Baxter's Medical Information Service at 1-800-933-0303.

To place an order, please contact Baxter's Center for Service by calling 1-888-229-0001.

To report product quality issues please contact Baxter Product Surveillance at 1-800-437-5176.

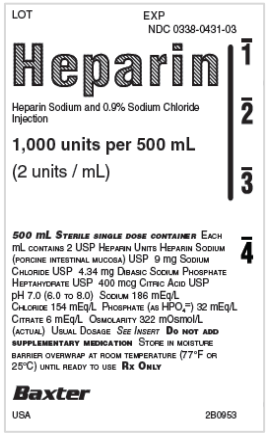
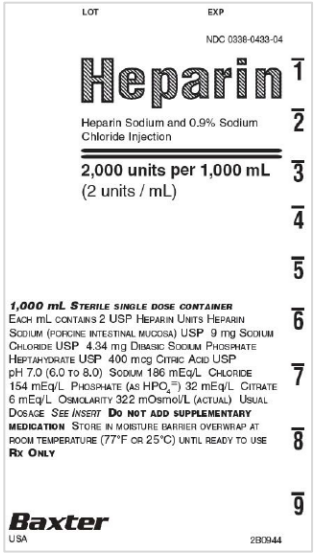
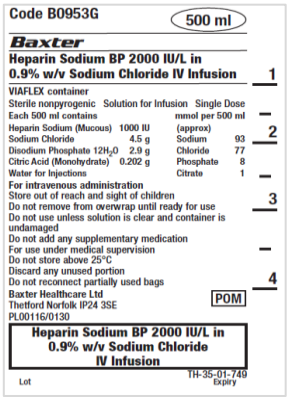
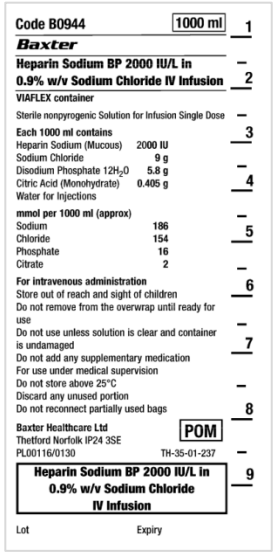
To report adverse events associated with these imported products, please call Baxter at 1-866-888-2472, or fax: 1-800-759-1801. Adverse events or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax:

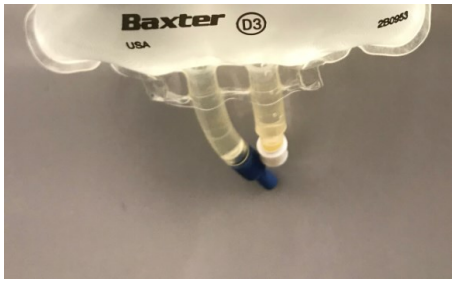
- Complete and submit the report **Online**: www.fda.gov/medwatch/report.htm

- **Regular mail or Fax**: Download form http://www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

Sincerely,

Dennis Vaughn
Vice President, Marketing Operations
Baxter Healthcare Corporation

	US FDA approved product	Import Product
	Heparin Sodium and 0.9% Sodium Chloride Injection	**Heparin Sodium BP 2,000 IU/L in 0.9% w/v Sodium Chloride IV Infusion**
	 	 
Ingredients	Each 500 mL contains 1,000 units Heparin Sodium (porcine Intestinal Mucosa) USP, 4.5g Sodium Chloride USP, 2.17 g Dibasic Sodium phosphate Heptahydrate USP, 0.2 g Citric Acid USP Each 1000 mL contains 2,000 units Heparin Sodium (porcine Intestinal Mucosa) USP, 9g Sodium Chloride USP, 4.34 g Dibasic Sodium phosphate Heptahydrate USP, 0.4 g Citric Acid USP	Each 500 mL contains 1,000IU Heparin Sodium (Mucous), 4.5 g Sodium Chloride, 2.9 g Disodium Phosphate $12H_2O$, 0.202 g Citric Acid (Monohydrate), Water for Injection Each 1,000 mL contains 2,000 IU Heparin Sodium (Mucous), 9.0 g Sodium Chloride, 5.8 g Disodium Phosphate $12H_2O$, 0.405 g Citric Acid (Monohydrate), Water for Injection
Additional Information	Each 500 mL and 1000 mL container contains: Sodium 186 mEq/L; Chloride 154 mEq/L; Phosphate (as $HPO_4=$) 32 mEq/L; Citrate 6 mEq/L pH 7.0 (6.0 to 8.0); Osmolarity 322 mOsmol/L	Mmol per 500 mL (approx.) Sodium 93 Chloride 77 Phosphate 8 Citrate 1 Mmol per 1000 mL (approx.) Sodium 186 Chloride 154 Phosphate 16 Citrate 2
Description	Heparin Sodium and 0.9% 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.	Sterile non pyrogenic aqueous solution intended for intravenous administration.
Administration ports	Medication port with rubber closure PLUS Administration port with pull off port protector	Administration port with Twist off Protector (No medication port)

	US FDA approved product	Import Product
	Heparin Sodium and 0.9% Sodium Chloride Injection	**Heparin Sodium BP 2,000 IU/L in 0.9% w/v Sodium Chloride IV Infusion**
		
Indication	Heparin Sodium and 0.9% Sodium Chloride Injection at a concentration of 2 units/mL is indicated as an aid in the maintenance of catheter patency	Heparin sodium in 0.9% Sodium Chloride infusion is indicated as an anticoagulant in extra corporeal circulation and dialysis procedures, and as an aid in the maintenance of catheter patency.
Dosage and administration	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. **Maintenance of Catheter Patency** Although the rate for infusion of the 2 units/mL formulation is dependent upon age, weight, clinical condition of the patient and the procedure being employed, an infusion rate of 3 mL/hour has been found to be satisfactory. 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 and 0.9% Sodium Chloride Injection.**	Dosage of heparin should be titrated against patient response. **Heparinisation for dialysis procedures** Dosage is dependent upon the age, weight and clinical condition of the patient. It is suggested that a proper heparinisation schedule is used before, and maintained throughout the procedure to prevent clotting and subsequent blood path obstruction. **Maintenance of Catheter Patency** The dosage should be adapted to catheter characteristics and the clinical condition of the patient. **Administration** Administration is by intravenous infusion. *Elderly patients* A higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Clinical studies indicate that lower doses of heparin may be indicated in these patients.
Contraindica-tions	Heparin sodium should not be used in patients: With severe thrombocytopenia; In whom suitable blood coagulation tests - e.g., the whole-blood clotting time, partial thromboplastin time, etc. - cannot be performed at appropriate intervals (this contraindication refers to full-dose heparin; there is usually no need to monitor coagulation parameters in patients receiving low-dose heparin); With an uncontrollable active bleeding state (see **Warnings**), except when this is due to disseminated intravascular coagulation.	**Contraindications** Heparin sodium should not be used in patients: • with a history of hypersensitivity to heparin • with severe thrombocytopenia • with an uncontrollable active bleeding state such as haemophilia, except when this is due to disseminated intravascular coagulation
Warnings and Precautions	**See manufacturer's package insert for full prescribing information.** **Hypersensitivity** Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations. **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 hemorrhagic event. Heparin sodium should be used with extreme caution in disease states in which there is increased danger of hemorrhage. **Coagulation Testing** When heparin sodium is administered in therapeutic amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is unduly prolonged or if hemorrhage occurs, heparin sodium should be discontinued promptly (see Overdosage). **Thrombocytopenia** Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of up to 30%. Platelet counts should be obtained at baseline and periodically during heparin administration. Mild thrombocytopenia (count greater than 100,000/mm3) may remain stable or reverse even if heparin is continued.	**Special warnings and precautions for use** The intravenous administration of solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the injections. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of the injections. Excessive administration of potassium free solutions may result in significant hyperkalaemia. Heparin Sodium BP in 0.9% Sodium Chloride intravenous infusion must be used with caution in patients who have impaired ability to handle sodium, such as renal insufficiency and congestive heart failure, and in clinical states in which there exists oedema with sodium retention. Do not use unless solution is clear and container undamaged. Heparin sodium BP in 0.9% w/v sodium chloride intravenous infusion should not be administered orally. Heparin should be used with extreme care in patients suffering from conditions in which there is an increased danger of haemorrhage. Haemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in haematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of haemorrhagic event. Heparin sodium should be used with extreme caution in disease states in which there is increased

	US FDA approved product	Import Product
	Heparin Sodium and 0.9% Sodium Chloride Injection	**Heparin Sodium BP 2,000 IU/L in 0.9% w/v Sodium Chloride IV Infusion**
	However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100,000/mm3 or if recurrent thrombosis develops (see Heparin-induced Thrombocytopenia (HIT) With or Without Thrombosis), the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered. **Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis)** HIT is a serious immune-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as HIT with thrombosis. Thrombotic events may also be the initial presentation for HIT. Once HIT (with or without thrombosis) is diagnosed or strongly suspected, all heparin sodium sources (including heparin flushes) should be discontinued and an alternative anticoagulant used. Future use of heparin sodium, especially within 3 to 6 months following the diagnosis of HIT (with or without thrombosis), and while patients test positive for HIT antibodies, should be avoided. **Delayed Onset of HIT (With or Without Thrombosis)** Heparin-induced thrombocytopenia (with or without thrombosis) 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 (with or without thrombosis). **PRECAUTIONS General** Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) and Delayed Onset of HIT (With or Without Thrombosis). Heparin Resistance: Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients. Increased Risk in Older Patients, Especially Women: A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age. Solutions Containing Sodium: These solutions should be used with caution in patients receiving corticosteroids or corticotropin. **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 (see Dosage and Administration). **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. **Pregnancy** Teratogenic Effects - Pregnancy Category C: Animal reproduction studies have not been conducted with heparin sodium. It is 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. See Dosage and Administration. **Geriatric Use** A higher incidence of bleeding has been reported in patients over 60 years of age, especially women (see Precautions, General). Clinical studies indicate that lower doses of heparin may be indicated in these patients (see Precautions, General and Clinical Pharmacology). Do not administer unless solution is clear and seal is intact.	danger of haemorrhage. Some of the conditions in which increased danger of haemorrhage 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. Haematologic - Conditions associated with increased bleeding tendencies, such as haemophilia, thrombocytopenia, and some vascular purpuras. Gastrointestinal - Ulcerative lesions and continuous tube drainage of the stomach or small intestine. Other - Menstruation, liver disease with impaired haemostasis. Periodic hematocrit tests, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration. Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium, or taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and in all patients treated for more than 7 days. Thrombocytopenia is commonly seen in patients receiving heparin. 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, the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered. HIT is a serious immune-mediated disorder resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as HIT with thrombosis. Thrombotic events may also be the initial presentation for HIT. 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 fatal outcomes. Once HIT (with or without thrombosis) is diagnosed or strongly suspected, heparin sodium (including heparin flushes) should be discontinued and an alternative anticoagulant used. Future use of heparin sodium, especially within 3 to 6 months following the diagnosis of HIT (with or without thrombosis), and while patients test positive for HIT antibodies, should be avoided. Elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have been commonly seen in patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution. Resistance to heparin has been noted in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients. These solutions should be used with caution in patients receiving corticosteroids or corticotropin. **Pregnancy:** The safety of heparin sodium in 0.9% w/v Sodium Chloride intravenous infusion has not been demonstrated in pregnant women. There are no or limited amount of data from the use of Heparin Sodium in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Heparin Sodium is not recommended during pregnancy. **Breast-feeding:** Heparin does not pass the placental barrier; it is not excreted in human milk. Heparin Sodium can be used during breast-feeding.
Drug Interactions	**See manufacturer's package insert for full prescribing information.** 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	**Interaction with other medicinal products and other forms of interaction** Heparin may prolong the one stage prothrombin time. Accordingly, when Heparin is given with dicoumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose of heparin should elapse before blood is drawn, if a valid prothrombin time is to be

<table>
<tr><th></th><th>US FDA approved product</th><th>Import Product</th></tr>
<tr><th></th><th>Heparin Sodium and 0.9% Sodium Chloride Injection</th><th>Heparin Sodium BP 2,000 IU/L in 0.9% w/v Sodium Chloride IV Infusion</th></tr>
<tr><td></td><td>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.

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.

Drug/Laboratory Tests Interactions Hyperaminotransferasemia Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.</td><td>obtained.

Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others which interfere with platelet aggregation (the main haemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients on heparin therapy.

The use of ACE inhibitors and angiotensin-II antagonists in conjunction with heparin increase the risk of hyperkalaemia.
Incompatibilities Do not add other drugs to Heparin Sodium in 0.9% Sodium Chloride Intravenous Infusion.</td></tr>
<tr><td>**Adverse Events**</td><td>**See manufacturer's package insert for full prescribing information.**
Hemorrhage Hemorrhage is the chief complication that may result from heparin therapy (see Warnings). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see Overdosage). **It should be appreciated that 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 hemorrhage complications may be difficult to detect: Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal hemorrhage and insufficiency. Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short or long-term anticoagulant therapy. This complication if unrecognized may be fatal.
Retroperitoneal hemorrhage.
Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) and Delayed Onset of HIT (With or Without Thrombosis). See WARNINGS.
Local Irritation Local irritation, erythema, mild pain, hematoma or ulceration may follow deep subcutaneous (intrafat) injection of heparin sodium. These complications are much more common after intramuscular use, and such use is not recommended.
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, Precautions.)</td><td>The most frequently reported undesirable effects are bleeding events, reversible increase in liver enzymes, thrombocytopenia and various skin reactions. Allergic reactions, skin necrosis and priapism have also been reported. The following adverse reactions have been observed and reported during treatment with Heparin Sodium with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (<1/10 000), not known (cannot be estimated from available data).
Adverse Drug Reactions
<table>
<tr><th>System Organ Class (SOC)</th><th>MedDRA Preferred Term</th><th>Frequency</th></tr>
<tr><td>Vascular disorders</td><td>Haemorrhage</td><td>Not known</td></tr>
<tr><td></td><td>Epistaxis</td><td>Not known</td></tr>
<tr><td></td><td>Contusion</td><td>Not known</td></tr>
<tr><td>Blood and lymphatic system disorders</td><td>Thrombocytopenia</td><td>Not known</td></tr>
<tr><td>Renal and urinary disorders</td><td>Haematuria</td><td>Not known</td></tr>
<tr><td>Endocrine disorders</td><td>Adrenal insufficiency</td><td>Not known</td></tr>
<tr><td></td><td>Hypoaldosteronism</td><td>Not known</td></tr>
<tr><td>Skin and subcutaneous tissue disorders</td><td>Alopecia</td><td>Not known</td></tr>
<tr><td></td><td>Skin necrosis</td><td>Not known</td></tr>
<tr><td>Musculoskeletal, connective tissue and bone disorders</td><td>Osteoporosis</td><td>Not known</td></tr>
<tr><td>Immune system disorders</td><td>Hypersensitivity</td><td>Not known</td></tr>
<tr><td>Metabolism and nutrition disorders</td><td>Rebound hyperlipemia</td><td>Not known</td></tr>
<tr><td></td><td>Hyperkalaemia</td><td>Not known</td></tr>
<tr><td>Reproductive system and breast disorders</td><td>Priapism</td><td>Not known</td></tr>
<tr><td>General disorders and administration site conditions</td><td>Injection site reaction,</td><td>Not known</td></tr>
<tr><td>Investigations</td><td>Alanine aminotransferase increased;
Aspartate aminotransferase increased</td><td>Not known</td></tr>
</table>
Haemorrhage: Haemorrhage is the chief complication that may result from heparin therapy. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug. **It should be appreciated that 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 haemorrhage complications may be difficult to detect.

Adrenal haemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal haemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.</td></tr>
</table>

	US FDA approved product	Import Product
	Heparin Sodium and 0.9% Sodium Chloride Injection	**Heparin Sodium BP 2,000 IU/L in 0.9% w/v Sodium Chloride IV Infusion**
		Ovarian (corpus luteum) haemorrhage developed in a number of women of reproductive age receiving short or long-term anticoagulant therapy. This complication if unrecognized may be fatal.
Overdose and Treatment	**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 the labeling of Protamine Sulfate Injection, USP products should be consulted.	**Overdose** Bleeding is the chief sign of heparin overdosage. Protamine Sulphate (1% w/v solution) by slow intravenous infusion will neutralise heparin. No more than 50 mg should be given very slowly in any 10 minute period. Each mg of protamine sulphate neutralises approximately 100 units of heparin (or 1 to 1.5 mg neutralises approximately 1 mg of heparin). Heparins derived from various animal sources require different amounts of protamine sulphate for neutralisation. Decreasing amounts of protamine are required as time from the last heparin injection increases. Thirty minutes after a dose of heparin, approximately 0.5 mg of protamine is sufficient to neutralise each 100 units of heparin. Blood or plasma transfusions may be necessary; these dilute but do not neutralise heparin.
Storage Conditions	Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. It is recommended the product be stored at room temperature (25°C); brief exposure up to 40°C does not adversely affect the product.	Keep out of the sight and reach of children. Do not store above 25°C. • Heparin Sodium Solution must not be used if the container is damaged or the solution is not clear.
Directions for Use	**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.	For use under medical supervision: The solution should only be used once. Any left over solution should be discarded. Do not use unless solution is clear and the container is undamaged. Discard any unused portion. Do not reconnect partially used bags.
How Supplied	Heparin Sodium and 0.9% Sodium Chloride Injection in VIAFLEX Plus plastic container is supplied in 500 mL and 1,000 mL bags of Heparin and 0.9% Sodium Chloride Injection as follows: 2B0953 Heparin Sodium 1,000 units in 0.9% Sodium Chloride (500 mL) NDC 0338-0431-03 2B0944 Heparin Sodium 2,000 units in 0.9% Sodium Chloride (1,000 mL) NDC 0338-0433-04	It is supplied as a clear solution for infusion (slow injection) in a 500 ml and 1,000 mL VIAFLEX plastic bag with a plastic overpouch. Do not remove from overpouch until ready for use. FKB0953G Heparin Sodium BP 2,000 IU /L in 0.9% w/v Sodium Chloride IV Infusion (1,000 IU/500 mL) NDC 0338-9556-20 FKB0944G Heparin Sodium BP 2,000 IU /L in 0.9% w/v Sodium Chloride IV Infusion (2000 IU/1,000 mL) NDC 0338-9552-10