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-β-D-glucose 6-sulfate, (3) β-D-glu-
curononic 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 sul-
fate and carboxylic acid groups. In heparin
sodium, the acidic protons of the sulfate units
are partially replaced by sodium ions.
Heparin Sodium Injection, USP is a sterile
preparation of heparin sodium derived from
porcine intestinal mucosa, standardized for
anticoagulant activity, in water for injection.
It is to be administered by intravenous or deep
subcutaneous routes. The potency is deter-
mmed by a biological assay using a USP refer-
ence standard based on units of heparin activ-
ity per milligram.

Structure of Heparin Sodium (representative subunits):

Each mL contains: 5,000 USP Heparin Units
(porcine); 6 mg sodium chloride; 15 mg benzy1
alcohol (as a preservative). Hydrochloric acid
and/or sodium hydroxide may have been added for
pH adjustment (5.0-7.5).

CLINICAL PHARMACOLOGY:
Heparin inhibits reactions that lead to the clot-
ting of blood and the formation of fibrin clots.
In vivo and in vitro, Heparin acts at multi-
ple sites in the normal coagulation sys-
tem. 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 devel-
oped, larger amounts of heparin can inhibit fur-
ther coagulation by inactivating thrombin
and preventing the conversion of fibrinogen to
fibrin. Heparin also prevents the formation of a sta-
bile fibrin clot by inhibiting the activation of the fibrin
stabilizing factor.

Bleeding time is usually unaffected by hep-
arin. Clotting time is prolonged by full thera-
paeutic doses of heparin sodium; in most cases
it is not measurably affected by low doses
of heparin.

Patients over 60 years of age, following simi-
lar doses of heparin, may have higher plasma
levels of heparin and longer activated partial
thromboplastin times (APTTs) compared with
patients under 80 years of age.

Peak plasma levels of heparin are achieved two
to four hours following subcutaneous administration, although there are considerable individual vari-
ations. Loglinear plots of heparin plasma con-
centrations 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 biotransfor-
mation. The biphasic elimination curve, a rapidly
declining alpha phase (1/2 = 10 minutes) and
after the age of 40 a slower beta phase, indi-
cates uptake in organs. The absence of a rela-
tionship between anticoagulant half-life and
centration half-life may reflect factors such as
protein binding of heparin.

Heparin does not have fibrinolytic activity; there-
fore, it will not lyse existing clots.

INDICATIONS AND USAGE:
Heparin Sodium Injection is indicated for:
Anticoagulant therapy in prophyaxis and treat-
mant of venous thrombosis and its extension;
Low-dose regimen for prevention of postopera-
tive deep venous thrombosis and pulmonary
embolism in patients undergoing major abdo-
minothoracic surgery or who, for other reasons
are at risk of developing thromboembolic dis-
ease (see DOSAGE AND ADMINISTRATION);
Prophyaxis and treatment of pulmonary embolism;

Atrophic fibrillation with embolization;
Diagnosis and treatment of acute and chronic
consumptive coagulopathies (disseminated
intravascular coagulation).
Prevention of clotting in arterial and cardiac
surgery;
Prophyaxis and treatment of peripheral arter-
ial embolism.
Heparin may also be employed as an antico-
agulant in blood transfusions, extracorporeal
circulation, dialysis procedures and in blood
samples for laboratory tests.

CONTRAINDICATIONS:
Heparin sodium should NOT be used in patients
with the following conditions:
Severe thrombocytopenia; suitable blood coagu-
lation tests e.g., the whole-blood clotting time,
partial thromboplastin time, etc. cannot be per-
formed at adequate heparin dosage; Contraindica-
tion refers to full-dose heparin; there is usually
no need to monitor coagulation parameters in
patients receiving low-dose heparins.

An uncontrollable active bleeding state (see
WARNINGS), except when this is due to dis-
seminated intravascular coagulation.

WARNINGS:
Heparin is not intended for intramuscular use.
Do not use Heparin Sodium Injection as a “cath-
er lock flush” product.

Fatal Medication Errors
Heparin Sodium Injection is supplied in vials
containing various strengths of heparin, includ-
ing vials that contain a highly concentrated
solution of 10,000 units in 1 mL. Fatal hemor-
rhages have occurred in pediatric patients due
to medication errors in which 1 mL Heparin
Sodium Injection vials were confused with
1 mL “catheter lock flush” vials. Carefully examine
each Heparin Sodium Injection vial to confirm
the correct vial choice prior to administration
of the drug.

Hypersensitivity
Patients with documented hypersensitivity to
heparin sodium 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
cautions in disease states in which there is
increased danger of hemorrhage. Some of the
conditions in which increased danger of hem-
orrhage exists are:
Cardiovascular—Subacute bacterial endocar-
ditis, 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 hemo-
philia, thrombocytopenia and some vascular
purpuras.
Gastrointestinal—Ulcereative lesions and con-
tinuous tube drainage of the stomach or small
intestine.
Other—Menstruation, liver disease with impaired
hemostasis.

Coagulation Testing
When heparin sodium is administered in ther-
apeutic amounts, its dosage should be regu-
lated by frequent testing. If the coagulation test is
unduly prolonged or if hemorrhage occurs, heparin sodium should be promptly discontinued (see OVERDOSE).

Thrombocytopenia
Thrombocytopenia has been reported to occur in
patients receiving heparin with a reported inci-
dence 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.
However, thrombocytopenia of any degree
should be monitored closely. If the platelet
count falls below 100,000/mm³ or if recurrent
thrombocytopenia 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 in death of 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 HIT. In serious thrombotic events including 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 noted closely. If the counts fall below 100,000/mm3 or if recurrent thrombo­sis develops, the heparin product should be stopped. Patients with confirmed or suspected anticoagulants considered if patients require continued anticoagulation.

Delayed Onset of HIT or 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

Carefully examine all Heparin Sodium Injection vials for the presence of the correct strength prior to administration of the drug. Pediatric patients, including neonates, have died as a result of errors in which Heparin Sodium Injection vials have been confused with “catheter lock flush” vials (see WARNINGS, Fatal Medication Errors). This product contains the preservative benzyl alcohol and is not recommended for use in neonates. When benzyl alcohol has been reported to be fatal ‘gassing syndrome’ in neonates (children less than one month of age) following the administration of parenteral injections containing the preservative benzyl alcohol. Symptoms include a strik­ong onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

PRECAUTIONS:

General

Thrombocytopenia, Heparin-induced Thrombocytopenia and Thrombocytopenia and Thrombosis (HITT)

Heparin Resistance—Increased resistance to heparin sodium is frequently encountered in fever, thrombosis, thrombophlebitis, infections with multiple or severe complications, myocardial infarction, cancer, and in postoperative patients. 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 sodium therapy, rather than merely during administration (see DOSEAGE AND ADMINISTRATION).

Drug Interactions

Oral Anticoagulants—Heparin sodium may pro­duce an adverse effect on the prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin, a period of at least 24 hours after the last intravenous dose or 24 hours after the last subcutaneous dose should elapse before blood tests are obtained, if a valid prothrombin time is to be obtained.

Platelet Inhibitors—Drugs such as acetylsalicylic acid, dextran, phenoxybenzamine, isoproterenol, indomethacin, dipryramide, hydrocortisone, and quinidine and other interfer with platelet aggregation reactions (the main hemostatic deficiencies in heparinized patients) may impair bleeding and should be used with caution in patients receiving heparin sodium.

Oral Antituberculosis Drugs—Digi­tals, tetracyclines, ni­cotine or antihistamines may partially counteract the anticoagulant action of heparin sodium. Intrave­nous heparin administered to heparinized patients may result in a decrease of the partial thromboplastin time with subsequent rebound effect, and heparin therapy should be continued for at least 24 hours after discontinuation of partial thromboplastin time and adjustment of heparin dosage are recommended during coadministration of heparin and intravenous nitroglycerin.

Drug/Laboratory Tests Interactions

Hyperaminotransferasemia—Significant eleva­tions of aspartate transaminase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since aminotransfer­ase determinations are important in the dif­ferential diagnosis of myocardial infarction, liver disease and other serious conditions, increases that might be caused by drugs (like heparin) should be interpreted with caution.

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

See DOSEAGE AND ADMINISTRATION, Pedi­atric Use.

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 heparin may be indicated in these patients (see CLINICAL PHAR­MACOLOGY and DOSEAGE AND ADMINIS­TRATION).

ADVERSE REACTIONS:

Hemorrhage

Hemorrhage is the chief complication that may result from heparin therapy (see WARNINGS). An overly prolonged clotting time or minor bleeding during therapy may be controlled by withdrawing the drug (see OVERDOSE). 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 hemorrhagic com­plications may be difficult to detect:

(a) Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treat­ment should be discontinued in patients who develop abdominal tenderness, signs or symptoms of acute adrenal hemorrhage and insufficiency. Ini­tiation of corrective therapy should not depend on diagnostic confirmations of the diagnosis, since any delay in an acute situa­tion may result in the patient’s death.

(b) Ovarian (intraperitoneal) hemorrhage devel­oped in a number of women of reproduc­tive age who were given long-term anticoagulant therapy. This complication, if unrecognized, may be fatal.

(c) Retropertioneal hemorrhage.

Thrombocytopenia, Heparin-induced Thrombocy­topenia and Heparin-induced Thrombocytopenia and Thrombosis (HITT) and Delayed Onset of HIT and HITT

See WARNINGS.

Local Irritation

Local irritation, erythema, mild pain, hematoma or ulceration may occur after subcutaneous (in­tratrap) injection of heparin sodium. These com­plications are much more common after intra­muscular use, but they can occur after intra­venous injection. Intravenous infusion, or deep subcutaneous (intrafet, i.e., above the iliac crest or abdominal fat layer) injection. Although the intramuscular route of administration should be avoided because of the frequent occurrence of hematomas at the injection site.

The dosage of heparin sodium should be adjusted according to the patient’s coagulation test results. When heparin sodium is given in continuous intravenous infusion, the coagula­tion time should be determined approximately every four hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection, coagulation tests should be performed before each patient’s first dose of heparin and at early stages of treatment and at appropriate inter­vals thereafter. Dosage is adjusted as desirable which the activated partial prothromboplastin time (APTT) is 1.5 to 2 times normal or when the whole blood clotting time is elevated approximately 2.5 to 3.3 times the control value (or similar type is to be begun in patients already receiving heparin sodium, baseline and subse­quent tests of prothrombin time are to be determined at a time when heparin sodium activity is too low to affect the prothrombin time. This is about five hours after the last dose and 24 hours after the last subcutaneous dose. If continuous IV heparin sodium is used, prothrombin time can usually be measured at any time.

Conversion to Oral Anticoagulant

When an oral anticoagulant of the coumarin or similar type is to be begun in patients already receiving heparin sodium, baseline and sub­sequent tests of prothrombin time are to be determined at a time when heparin sodium activity is too low to affect the prothrombin time. This is about five hours after the last dose and 24 hours after the last subcutaneous dose. If continuous IV heparin sodium is used, prothrombin time can usually be measured at any time.
In converting from heparin sodium to an oral anticoagulant, the dose of the oral anticoagu­lant should be the usual initial amount and there­after prothrombin time should be determined at the usual intervals. To ensure continuous anti­coagulation, it is advisable to continue full hepa­rin sodium therapy for several days after the prothrombin time has reached the therapeutic range. Heparin sodium therapy may then be discontinued without tapering.

**Therapeutic Anticoagulant Effect With Full­Dose Heparin**

Although dosage must be adjusted for the individual patient according to the results of suitable laboratory tests, the following dosage schedules may be used as guidelines:

<table>
<thead>
<tr>
<th>METHOD AND ADMINISTRATION</th>
<th>FREQUENCY</th>
<th>RECOMMENDED DOSE (based on 150 lb [68 kg] patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Subcutaneous Injection</td>
<td>Initial Dose</td>
<td>5,000 units by IV injection, followed by 10,000 to 20,000 units of a concentrated solution, subcutaneously</td>
</tr>
<tr>
<td>Continuous</td>
<td>20,000 to 40,000 units/24 hours or 1,000 mL of 0.9% Sodium Chloride Injection, USP or in any compatible solution for infusion</td>
<td></td>
</tr>
</tbody>
</table>

**Pediatric Use**

Follow recommendations of appropriate pedia­tric reference texts. In general, the following dosage schedule may be used as a guideline:

<table>
<thead>
<tr>
<th>METHOD</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Dose</td>
<td>50 units/kg (IV, infusion)</td>
</tr>
<tr>
<td>Maintenance Dose</td>
<td>100 units/kg (IV, infusion) every four hours, or 20,000 units/m²/24 hours continuously</td>
</tr>
</tbody>
</table>

**Geriatric Use**

Patients over 60 years of age may require lower doses of heparin.

**Surgery of the Heart and Blood Vessels**

Patients undergoing total body perfusion for open-heart surgery should receive an initial dose of not less than 150 units per kilogram. Fre­quently, a dose of 300 units of heparin sodium per kilogram of body weight is used for proce­dures estimated to last less than 60 minutes, or 400 units per kilogram for those estimated to last longer than 80 minutes.

**Low-Dose Prophylaxis of Postoperative Thromboembolism**

A number of well-controlled clinical trials have demonstrated that low-dose heparin prophylaxis, given just prior to and after surgery, will reduce the incidence of postoperative deep vein thrombosis in the legs (as measured by the I-125 fibrinogen technique and venography) and of clinical pulmonary embolism. The most widely used dosage has been 5,000 units 2 hours before surgery and 5,000 units every 6 to 12 hours there­after for seven days or until the patient is fully ambulatory, whichever is longer. The heparin is given by deep subcutaneous injection in the arm or anterior thigh with a fine needle (25 to 26 gauge) to minimize tissue trauma. A concentrated solu­tion of heparin sodium is recommended. Such prophylaxis should be reserved for patients over the age of 40 who are undergoing major surgery. Patients with bleeding disorders and those hav­ing neurosurgery, spinal anesthesia, eye surgery or potentially sanguineous operations should be excluded, as well as patients receiving oral anticoagulants or platelet-active drugs (see WARNINGS). The value of such prophylaxis in hip surgery has not been established. The possibility of increased bleeding during surgery or postoperatively should be borne in mind. If such bleeding occurs, discontinuance of heparin and neutralization with protamine sulfate are advisable. If clinical evidence of thrombo­embolism develops despite low-dose prophylaxis, full therapeutic doses of anticoagulants should be given unless contraindicated. All patients should be screened prior to hepariniza­tion to rule out bleeding disorders, and moni­