CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 18-609/S-033

Name: Heparin Sodium in 0.9% Sodium Chloride Injection in Plastic Container

Sponsor: Baxter Healthcare Corporation

Approval Date: August 21, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-609/S-033

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-609/S-033

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-609/S-033
NDA 18-609/S-035

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Vice President, Regulatory Affairs I.V. Systems Division
Route 120 and Wilson Road; RLT-10
Round Lake, IL 60073-0490

Dear Ms. Marconi:

Please refer to your supplemental new drug applications dated May 8, 2001, received May 10, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium in 0.9% Sodium Chloride in Plastic Container, PL 146®.

We acknowledge receipt of your submission dated May 8, 2001. Your submission of May 8, 2001 constituted a complete response to our April 30, 1999 and October 14, 1999 action letters.

These supplemental new drug applications provide for labeling to comply with the Final Rules entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling" published in the December 13, 1994 Federal Register, and "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of Geriatric Use Subsection in the Labeling" published in the August 27, 1997 Federal Register.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted May 8, 2001). Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Cheryl Perry, Regulatory Health Project Manager, at (301) 827-7475.

Sincerely,

{See appended electronic signature page}

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lilia Talarico
8/21/01 06:34:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-609/S-033

APPROVABLE LETTER

APR 30 1999

NDA 18-609/S-033

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

Dear Ms. Marconi:

Please refer to your supplemental new drug application dated December 23, 1998, received December 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection in 0.9% Sodium Chloride in Plastic Container, PL 146®.

This supplement proposes the following changes: (1) in the PRECAUTIONS section, the "Pediatric Use" subsection, in response to the Final Rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling," published in the December 13, 1997 Federal Register, the addition of the following sentence: [redacted] and (2) in the DOSAGE AND ADMINITRATION section, the addition of the following information:

[redacted]

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to:

1. Submit draft printed labeling revised as follows:

   a. In the PRECAUTIONS section, the "Pediatric Use" subsection:

      Safety and effectivess in pediatric patients have not been established.

      See **Dosage and Administration.**

      Do not administer unless solution is clear and seal is intact.

b. In the DOSAGE AND ADMINSTRATION section, in the "Maintenance of Catheter Patency" subsection, **delete** the second paragraph of the subsection:

[ ]

2. Alternatively, provide the following information supporting the proposed changes: (a) a description of the safety and effectiveness results of each of the studies submitted December 23, 1998; (b) an overall risk/benefit analysis supporting the proposed labeling changes; and (c) annotated labeling citing the specific supportive source(s).

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Karen Oliver, Project Manager, at (301) 827-7310.

Sincerely,

4-29-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 18-609/S-033
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/J.Schmeling
HFD-95/DDMS
DISTRICT OFFICE

Drafted by: KO/April 29, 1999 K.Oliver 04/29/99
final: KO/04/29/99/c:\mydocuments\NDA18609-S-033-04-29-99-AE-pediatric

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-609/S-033

LABELING

Baxter

Heparin Sodium and 0.9% Sodium Chloride Injection

in Plastic Container

Viaflex® Plus Container

APPROVED

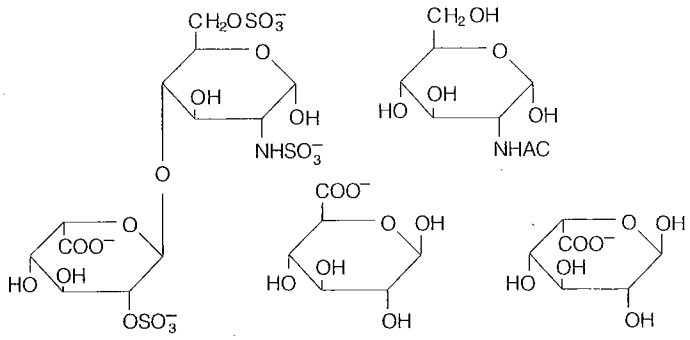
AUG 21 2001

Labeling: SLR033/035 A
NDA No: 18-609 Re'd. 5801
Reviewed by: Cherry 8/21/01 AP

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.

Structure of Heparin Sodium (representative subunits):



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

...n Sodium and 0.9% Sodium Chloride Injection is a buffered, sterile, nonpyrogenic solution of ...parin 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

	Size (mL)	Composition: Heparin Sodium, USP (units/mL)	Composition: Sodium Chloride, USP (NaCl) (g/L)	Composition: Dibasic Sodium Phosphate Heptahydrate, USP ($Na_2HPO_4 \cdot 7H_2O$) (g/L)	Composition: Citric Acid Hydrous, USP ($C_6H_8O_7 \cdot H_2O$) (g/L)	*Osmolarity (mOsmol/L) (actual)	pH	Ionic Concentration (mEq/L): Sodium	Chloride	Phosphate (as $HPO_4^{=}$)	Citrate
1000 USP Heparin Units and 0.9% Sodium Chloride Injection	500	2	9	4.34	0.4	322	7.0 (6.0 to 8.0)	186	154	32 (16 mmol/L)	6
2000 USP Heparin Units and 0.9% Sodium Chloride Injection	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.

...cal Pharmacology

...in 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.

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 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.

Contraindications

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.

Warnings

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. 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.

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 0 to 30%. 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 count falls below 100,000/mm³ or if recurrent thrombosis develops (see White Clot Syndrome, **Precautions**), the heparin product should be discontinued. If continued heparin therapy is essential, administration of heparin from a different organ source can be reinstituted with caution.

Solutions containing sodium ion should be used with great care in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there exists edema with sodium retention.

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 hypokalemia.

In patients with diminished renal function, administration may result in sodium retention.

Precautions

1. General

a. White Clot Syndrome:

It has been reported that patients on heparin may develop new thrombus formation in association with thrombocytopenia resulting from irreversible aggregation of platelets induced by heparin, the so -called "white clot syndrome". The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

b. Heparin Resistance:

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

c. Increased Risk in Older Patients, Especially Women:

A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age

d. Solutions Containing Sodium:

These solutions should be used with caution in patients receiving corticosteroids or corticotropin.

2. 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**).

3. Drug Interactions

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.

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.

4. 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. 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.

5. 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.

6. 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.

7. Nursing Mothers

Heparin is not excreted in human milk.

8. Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

See **Dosage and Administration**.

9. 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.

Adverse Reactions

1. 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:

a. 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. 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.

b. 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.

c. Retroperitoneal hemorrhage.

2. 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.

3. 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.

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 - 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, Precautions**.)

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

4. Miscellaneous

Osteoporosis following long-term administration of high-doses of heparin, 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. 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.

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 the labeling of Protamine Sulfate Injection, USP products should be consulted.

Dosage and Administration

Heparin sodium is not effective by oral administration and Heparin Sodium and 0.9% Sodium Chloride Injection should not be given orally.

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.

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.

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.**

How Supplied

Heparin Sodium and 0.9% Sodium Chloride Injection in Viaflex® Plus plastic container is supplied as follows:

Code	Size (mL)	NDC	Product Name
2B0953	500	0338-0431-03	1000 USP Heparin Units and 0.9% Sodium Chloride Injection
2B0944	1000	0338-0433-04	2000 USP Heparin Units and 0.9% Sodium Chloride Injection

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.

Direction for Use of Viaflex® Plus Plastic Container

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. 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.

Baxter Healthcare Corporation
Deerfield, IL 60015 USA

Printed in USA

*For Bar Code Position Only

071914716

7-19-14-716
Rev. September 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-609/S-033

LABELING REVIEWS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 18-609/S-033 APR 2 9 1999

Name of Drug: Heparin Sodium and 0.9% Dextrose Injection in Plastic Container, PL 146®

Sponsor: Baxter Healthcare Corporation

Material Reviewed

Submission Date(s): December 23, 1998

Receipt Date(s): December 28, 1998

Background and Summary Description: The supplement, submitted December 23, 1998, provides for: (1) in the PRECAUTIONS section, the "Pediatric Use" subsection, in response to the Final Rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling," published in the December 13, 1997 Federal Register, the addition of the following sentence: ——— ——— and (2) in the DOSAGE AND ADMINITRATION section, the addition of the following information: [ ] and (3) documentation supporting the proposed changes. The firm submitted mocked-up package insert labeling for the supplement.

Review

The marked-up, annotated copy of the draft labeling, identified as "7-19-2-298-Rev. November 1995" was compared to the labeling, identified as "7-19-2-298 Rev. November 1995", submitted June 28, 1998 in annual report 018. The package inserts are identical except for the following:

Package Insert

1. In the PRECAUTIONS section, the "Pediatric Use" subsection, the text has been changed

   from:

   See **Dosage and Administration.**

Do not administer unless solution is clear and seal is intact.

to:

[ ]

See **Dosage and Administration.**

Do no administer unless solution is clear and seal is intact.

This revision UNACCEPTABLE (see Medical Officer's review dated April 27, 1999). The proposed subsection text should be deleted and replaced with the following:

Safety and effectivess in pediatric patients have not been established.

See **Dosage and Administration.**

Do not administer unless solution is clear and seal is intact.

2. In the DOSAGE AND ADMINSTRATION section, in the "Maintenance of Catheter Patency" subsection, the following information was inserted as the second paragraph of the subsection:

[ ]

This additional information is UNACCEPATBLE (see Medical Officer's review dated April 27, 1999).. The inserted information should be deleted.

Conclusions

The following changes are UNACCEPTABLE: 1 and 2.

Karen Oliver 04/29/99
Karen Oliver, RN, MSN
Regulatory Health Project Manager

Concur Kalenos 4-29-99

cc:
Original NDA 18-609/S-033
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/J.Schmeling
draft: KO/April 20, 1999
final: KO/04/29/99/c:\mydocuments\NDA18609-04-20-99-S-033-labrev

CSO REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 18-609/S-033, S-035

Name of Drug: Heparin Sodium and 0.9% Sodium Chloride Injection in Plastic Container, PL 146®

Sponsor: Baxter Healthcare Corporation

Material Reviewed

Submission Date: May 8, 2001

Receipt Date: May 10, 2001

Background and Summary Description:

Submission Dates	Purpose of Submissions	Action Dates	Action
S-033: December 23, 1998	Supplement 033 provides for changes in the PRECAUTIONS, "**Pediatric Use**" subsection of the package insert in response to the Final Rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling" published in the December 13, 1994 Federal Register.	April 30, 1999	Approvable
S-035: July 8, 1999	Supplement 035 provides for changes in the CLINICAL PHARMACOLOGY and the PRECAUTIONS ["General (Increased Risk in Older Patients)" and "**Geriatric Use**" subsections] sections of the package inserts in response to the Final Rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of Geriatric Use Subsection in the Labeling" published in the August 27, 1997 Federal Register.	October 14, 1999	Approvable
S-033 & S-035: May 8, 2001	Final printed labeling (FPL) in response to our approvable letters.	Pending	Recommend Approval

Review

Name of Drug	FPL Package Insert Identifier compared with →	Currently Approved Package Insert Identifier, submitted 29-Jun-00 in Annual Report-020; the draft labeling submitted 23-Dec-98 (S-033) and 8-Jul-99 (S-035).
Heparin Sodium and 0.9% Sodium Chloride Injection in Plastic Container	7-19-14-716 Rev. September 2000	7-19-2-298 Rev. November 1995

The package inserts are identical except for the following:

S-033: "PEDIATRIC USE" LABELING

Revised Section	Exact Location	Revised to:	Recommendation
PRECAUTIONS	*Pediatric Use:* subsection	"Safety and effectiveness in pediatric patients have not been established."	This revision, requested in the April 30, 1999 approvable letter, is **ACCEPTABLE.**
DOSAGE AND ADMINISTRATION	"Maintenance of Catheter Patency" subsection, second paragraph	DELETED paragraph proposed in draft labeling submitted on 23-Dec-98: [redacted]	This deletion, requested in the April 30, 1999 approvable letter, is **ACCEPTABLE.**

S-033: "GERIATRIC USE" LABELING

Revised Section	Exact Location	Revised to:	Recommendation
CLINICAL PHARMACOLOGY	third, stand-alone, paragraph	"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."	This revision, requested in the October 14, 1999 approvable letter, is **ACCEPTABLE.**

Revised Section	Exact Location	Revised to:	Recommendation
PRECAUTIONS	"General" subsection, "Increased Risk" sub-subsection	"**c. Increased Risk in Older Patients, Especially Women:** A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age."	This revision, requested in the October 14, 1999 approvable letter, is **ACCEPTABLE.**
PRECAUTIONS	"Geriatric Use" subsection	"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**)."	This revision, requested in the October 14, 1999 approvable letter, is **ACCEPTABLE.**
IDENTIFIER	Below HOW SUPPLIED section	From: 7-19-2-298 Rev.November 1995 To: 7-19-14-716 Rev. September 2000	This editorial change is **ACCEPTABLE.**

Conclusion

The identified labeling changes are acceptable, and an approval letter should be issued.

_____
Cheryl Perry, RN, BSN
Regulatory Health Project Manager

_____
Lilia Talarico, MD
Division Director

Draft: C. Perry/August 17, 2001
R/d Initials: L. Talarico/August 21, 2001
Final: N18609.s33.s35.LabRev.doc

CSO REVIEW

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/s/

Cheryl Perry
8/21/01 03:53:39 PM
CSO
NDA 18-609/S-033, S-035
CSO labeling review

Lilia Talarico
8/21/01 06:37:25 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-609/S-033

MEDICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

APR 27 1999

NDA:	18-609/SLR-033
Drug name:	Heparin Sodium in 0.9% Sodium Chloride in Plastic Container, PL 146®
Generic name:	Heparin Sodium USP; Sodium Chloride; USP.
Other names:	Heparin Sodium, Sodium Chloride
Sponsor:	Baxter Healthcare Corporation Round Lake, Illinois
Pharmacologic Category:	Anticoagulant
(Proposed) Indication(s):	Heparin Sodium and 0.9% Sodium Chloride Injection is indicated as an aid in the maintenance of catheter patency
Purpose of Submission:	This is a supplemental application that revises the Pediatric Use subsection of the label
Dosage Form(s)	1000 units/500 mL, and 2000 units/ 1000 mL
Route(s) of Administration:	Intravenous
Related reviews:	NDA 5,264/S-070 et al., March 5, 1997
Date of Submission: **Date received by HFD-180:** **Date of Review:**	December 23, 1998 December 28, 1998 April 22, 1999
Medical Reviewer:	John William Schmeling, M.D., Ph.D.

TABLE OF CONTENTS

LIST OF TABLES

ACRONYMS and ABBREVIATIONS

i.v.	Intravenous

1. MATERIAL UTILIZED IN REVIEW

1.1 Materials from NDA/IND

A single volume submission, stamp date December 23, 1998, was reviewed.

1.2 Related Review, Consults

Medical Officer's review of NDA: 5,264/S-070 et al., dated March 5, 1997, on pediatric labeling of heparin

2. BACKGROUND

The sponsor is making this submission in response to the Federal Register Notice of December 13, 1994 regarding: "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling; Final Rule."

The literature and clinical data relevant to the pediatric use of heparin was reviewed by a medical officer (March 5, 1997) and the class label was established.

3. MATERIAL SUBMITTED BY SPONSOR

The sponsor's submission is being submitted under 21CFR201.57(f)(9)(iii).

The sponsor has submitted the results of a literature search to support their proposed label changes.

The material has been presented in tabular form with accompanying references. Many details are given for each study, but there is no section for the results of the studies. Nor is there any discussion of the results of the studies.

At least two of the studies cited by the sponsor to support the safety and efficacy of heparin used for catheter patency were cited in the medical officer's review, done March 5 1997, of pediatric use of heparin flushes. The medical officer concluded that the benefit of heparin over saline alone

to maintain the patency of intravenous catheters in pediatric patients has not been established. (Smith et al. Maintenance of the patency of indwelling central venous catheters: is heparin necessary? Amer J Ped Hem Onc 1991; 13:141-3 and Kleiber et al. Heparin vs. saline for peripheral i.v. locks in children. Ped Nurs. 1993 19:405).

There is also no summary of the data with a risk/benefit assessment.

4. PROPOSED LABEL CHANGES

The sponsor's proposed changes are shown on the left side of Table 1.

4.1 Changes to Pediatric use section of the PRECAUTIONS section.

The sponsor proposes to add this sentence:

[ ]

The sponsor has not demonstrated this, the change is not acceptable.

4.2 Proposed changes to the DOSAGE AND ADMINISTRATION section of the label

The sponsor proposes to add this sentence:

[ ]

The sponsor has not indicated the source or reasoning for this change. It is not acceptable.

5. CONCLUSION

None of the sponsor's proposed changes are acceptable.

6. RECOMMENDATION

The sponsor is directed to the *Guidance for Industry, The Content and Format for Pediatric Use Supplements* and the *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications.*

In particular, the sponsor should include a conclusion section for each study in their table of studies. They should also include an overall analysis that include a risk/benefit

The changes recommended by the Medical Officer, which are consistent with the current class labeling, are approvable (See Table 1).

John W. Schmeling, M.D., Ph.D.

cc:
NDA 18-609/SLR-033
HFD-180
HFD-180/LTalarico LT 4-27-99
HFD-180/JSchmeling
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 4/27/99 jgw
N/18609904.JWS

Table 1: Label Summary

Proposed Label	Medical Officer's Recommendation
DESCRIPTION	
CLINICAL PHARMACOLOGY	
INDICATIONS AND USAGE	
CONTRAINDICATIONS	
WARNING	
PRECAUTIONS	
8. Pediatric use: [redacted] See Dosage and Administration Do not administer unless solution is clear and seal is intact	8. Pediatric use: Safety and effectiveness in pediatric patients have not been established See Dosage and Administration Do not administer unless solution is clear and seal is intact
ADVERSE REACTIONS	
DRUG ABUSE AND DEPENDENCE	
OVERDOSAGE	
DOSAGE AND ADMINISTRATION	
[redacted]	Maintenance of Catheter Patency: Although the rate for infusion of th 2 units/ml formulation is dependent upon age, weight, clinical conditio of the patient and the procedure being employed, an infusion rate of mL/hour has been found to be satisfactory.
HOW SUPPLIED	
ANIMAL PHARMACOLOGY AND/OR ANIMAL TOXICOLOGY	
CLINICAL STUDIES AND REFERENCES	
(Deletions are indicated with a strike through and additions are underlined)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-609/S-033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

I.V. Systems Division
Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

847.270.4637
Fax: 847.270.4668

Baxter

NDA NO. 18609 REF. NO. 033
NDA SUPPL FOR SLR
Pediatric

December 23, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180
Document Control Room #6B45
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 18-609 Heparin Sodium Injection in 0.9% Sodium Chloride in Plastic Container, PL 146®

Supplemental Application - Pediatric labeling

Ladies and Gentlemen:

Baxter Healthcare Corporation is submitting this supplemental application in response to the Final Rule published in the Code of the Federal Register on December 13, 1994 titled Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric use" Subsection in the Labeling, vol. 59, No. 238, pages 64240-64250.

The format and content of this supplemental application is consistent with the draft Guidance for Industry document titled "The Content and Format for Pediatric Use Supplements" dated March 1996.

If you have any questions, please contact me or Beth Esche at (847) 270-2577.

Sincerely,

Marcia Marconi /mbe

Marcia Marconi
Vice President, Regulatory Affairs
(847) 270-4637
(847) 270-4668 (FAX)

ORIGINAL

DEC 2 3 1998

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NDA 18-609/S-033

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Route 120 and Wilson Road
Round Lake, IL 60073-0490

DEC 30 1998

Dear Ms. Marconi:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Heparin Sodium in 0.9% Sodium Chloride in Plastic Container, PL 146®

NDA Number: NDA 18-609

Supplement Number: S-033

Therapeutic Classification: Standard

Date of Supplement: December 23, 1998

Date of Receipt: December 28, 1998

This supplement proposes the following changes: (1) in the PRECAUTIONS section, the "Pediatric Use" subsection, in response to the Final Rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling," published in the December 13, 1997 Federal Register, the addition of the following sentence: [redacted] and (2) in the DOSAGE AND ADMINITRATION section, the addition of the following information:

[redacted]

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 12, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug
Products, HFD-180
Attention: DOCUMENT CONTROL ROOM, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please contact me at (301) 827-7310.

Sincerely yours,

Karen Oliver, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 18-609/S-033
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/J.Schmeling

DISTRICT OFFICE

Drafted by: KO/December 30, 1998 K Oliver 12/30/98
Final: KO/12/30/98/c:\mydocuments\NDA18609-12-30-98-S-033-ackped

SUPPLEMENT ACKNOWLEDGEMENT (AC)