CENTRAL FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 18-609/S-035

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

Sponsor: Baxter Healthcare Corporation

Approval Date: August 21, 2001
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</tr>
</tbody>
</table>
APPLICATION NUMBER:
NDA 18-609/S-035

APPROVAL LETTER
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
APPLICATION NUMBER:
NDA 18-609/S-035

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

Dear Ms. Marconi:

Please refer to your supplemental new drug application dated July 8, 1999, received July 9, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium and 0.9% Sodium Chloride in Plastic Contain, PL 146®.

The supplemental application proposes the following change: the addition of a “Geriatric Use” subsection of the PRECAUTIONS section of the package insert to comply with 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 (Vol. 62, No. 166, pages 45313-45326).

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. In the DESCRIPTION section, delete the extra spacing in the last sentence of the first paragraph.

2. In the CLINICAL PHARMACOLOGY section, provide a third, stand-alone paragraph, to read:

   “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.”

3. In the PRECAUTIONS section, the “General” subsection, revise the “Increased Risk” sub-subsection to read:

   “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.”

4. In the PRECAUTIONS section, revise the “Geriatric Use” subsection to read:

   “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 maybe indicated in these patients (see PRECAUTIONS, General and CLINICAL PHARMACOLOGY).”

In addition, all previous revisions as reflected in the most recently approved package insert 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.
Please submit 20 copies of the printed labels and other labeling, ten of which are individually mounted on heavy-weight paper or similar material.

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 this 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 such action, FDA may proceed to withdraw this 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 this change prior to approval of this supplemental application.

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

Sincerely yours,

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-035
HFD-180/division file
HFD-094/DDMS
HFD-180/K.Oliver
HFD-180/K.Robie-Suh
HFD-180/L.Talarico
HFD-40/DDMAC (with labeling)
HFD-180/DNDC Division Director
DISTRICT OFFICE

Drafted by: A.Kacuba/October 7, 1999
Initialed by: K.Oliver/October 12, 1999, October 14, 1999
Final: AK/October 14, 1999
Filename: c:\wpfiles\18609-S-035-AE-letter.doc

APPROVABLE (AE)
Heparin Sodium and 0.9% Sodium Chloride Injection

in Plastic Container

Viaflex® Plus Container

Description

Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, usually named 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-sulfamido-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 usually in the order (3) > (5) > (1) = (4) > (2), 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 groups of the sulfate units are partially replaced by sodium ions.

Structure of Heparin Sodium (representative subunits):

![Structure of Heparin Sodium](image)

Composition

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

<table>
<thead>
<tr>
<th>Sodium</th>
<th>0.9% Sodium Chloride Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mEq/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>1000 U/mg</td>
</tr>
<tr>
<td>Potassium (as NaCl)</td>
<td>1000 U/mg</td>
</tr>
<tr>
<td>Chloride</td>
<td>1000 U/mg</td>
</tr>
</tbody>
</table>

*Normal physiologic osmolarity range is approximately 280 to 310 mOsml/L.*

Administration of substantially hypertonic solutions (≥ 600 mOsm/mL) 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 containers as well as by tissue culture toxicity studies.

Pharmacology

Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both in vitro and in vivo. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombins by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombin has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents 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 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 active thrombosis has developed, larger amounts of heparin can inhib...
2. Laboratory Tests

Periodic platelet counts, hematomas, 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, oral anticoagulants should be used with caution in patients receiving heparin sodium.

Platelet inhibitors: Drugs such as aspirin, 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

Hypoprothrombinemia:

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, tests 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.

Nursing Mothers

Heparin does not cross the placental barrier.

7. Nursing Mothers

Heparin is not excreted in human milk.

See Dosage and Administration.

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 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 hemorrhage complications may be difficult to detect:

- a. Arterial hemorrhage, with resultant acute arterial insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute arterial 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. Retropitoneal hemorrhage.

2. Local Irritation

Local irritation, erythema, mild pain, hematomas or ulceration may follow deep subcutaneous (intrathec) 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, rashes, tachycardia, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely.itching and burning, especially on the palmar side of the feet, may occur.

Pulmonary embolus 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 thromboembolism 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 pain, ischemic, and cyanosed limbs have in the past been attributed to vasoconstrictive reactions. Whether these are in fact identical to the thromboembolism 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, pruritus, and rebound hypercoagulability 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.

Overdose

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. Early bleeding 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 occur without any prior warning, 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.

Doseage 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 mUhour has been found to be satisfactory.

Periodic platelet counts, hematomas, 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:

<table>
<thead>
<tr>
<th>Code</th>
<th>Size (mL)</th>
<th>NDC</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2B0053</td>
<td>500</td>
<td>0338-0431-03</td>
<td>1000 USP Heparin Units and 0.9% Sodium Chloride Injection</td>
</tr>
<tr>
<td>2B0044</td>
<td>1000</td>
<td>0338-0433-04</td>
<td>2000 USP Heparin Units and 0.9% Sodium Chloride Injection</td>
</tr>
</tbody>
</table>

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 sterile may be impaired. Do not add supplementary medication.

Preparation for Administration

1. Suspend container from eyetlet support.

2. Remove plastic protector from outlet port at bottom of container.

3. Attach administration set. Refer to complete directions accompanying set.


7-19-14-716

Rev. September 2000

Baxter Healthcare Corporation

Deerfield, IL 60015 USA

Printed in USA

*For Bar Code Position Only

071914716
APPLICATION NUMBER:
NDA 18-609/S-035

LABELING REVIEWS
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 18-609/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: July 8, 1999

Receipt Date: July 9, 1999

Background and Summary Description: Heparin Sodium and 0.9% Sodium Chloride Injection is approved as an aid in the maintenance of catheter patency at a concentration of 2 units/mL. Supplement –035 provides for the addition of a “Geriatric Use” subsection in the PRECAUTIONS section of the package insert, to comply with 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 (Vol. 62, No. 166, pages 45313-45326).

Review

The submitted draft package insert, identified as “7-19-4-998 Rev. June 1999” was compared to the package insert, identified as “7-19-2-298 Rev. November 1995”, submitted June 28, 1999 in Annual Report –019. The following revisions were noted:

1. No changes have been made in the CLINICAL PHARMACOLOGY section.

Comment: This was found unacceptable in the medical officer review dated July 19, 1999 which recommends that the class labeling be used.

2. In the DESCRIPTION section, there is extra space interrupting the last sentence of the first paragraph.

Comment: This extra space should be deleted.

3. In the PRECAUTIONS section, the “General” subsection, no revisions have been made to the “Increased Risk” sub-subsection.

Comment: This was found unacceptable in the medical officer review dated July 19, 1999 which recommends that the class labeling be used.
4. In the Precautions section, a “Geriatric Use” subsection has been added to read:

   "9. Geriatric Use

[Blank space]

Comment: This was found unacceptable in the medical officer review dated July 19, 1999 which recommends that the class labeling be used.

5. The identifier has been revised from:


to:

   “7-19-4-998 Rev. June 1999”

Comment: This is an appropriate editorial revision.

Conclusions

The supplemental application is approvable. To be consistent with heparin lock flush class labeling, the firm should be requested to:

1. In the CLINICAL PHARMACOLOGY section, provide a third, stand-alone paragraph, to read:

   “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.”

2. In the PRECAUTIONS section, the “General” subsection, revise the “Increased Risk” sub-subsection to read:

   “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.”
3. In the PRECAUTIONS section, revise the “Geriatric Use” subsection to read:

“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 maybe indicated in these patients (see PRECAUTIONS, General and CLINICAL PHARMACOLOGY).”

4. In the DESCRIPTION section, delete the extra spacing in the last sentence of the first paragraph.
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:

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<th>Submission Dates</th>
<th>Purpose of Submissions</th>
<th>Action Dates</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-035: July 8, 1999</td>
<td>Supplement 035 provides for changes in the CLINICAL PHARMACOLOGY and the PRECAUTIONS [&quot;General (Increased Risk in Older Patients)&quot;] and &quot;Geriatric Use&quot; 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.</td>
<td>October 14, 1999</td>
<td>Approvable</td>
</tr>
<tr>
<td>S-033 &amp; S-035: May 8, 2001</td>
<td>Final printed labeling (FPL) in response to our approvable letters.</td>
<td>Pending</td>
<td>Recommend Approval</td>
</tr>
</tbody>
</table>
The package inserts are identical except for the following:

**S-033: “PEDIATRIC USE” LABELING**

<table>
<thead>
<tr>
<th>Revised Section</th>
<th>Exact Location</th>
<th>Revised to:</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECAUTIONS</td>
<td>Pediatric Use: subsection</td>
<td>“Safety and effectiveness in pediatric patients have not been established.”</td>
<td>This revision, requested in the April 30, 1999 approvable letter, is ACCEPTABLE.</td>
</tr>
<tr>
<td>DOSAGE AND ADMINISTRATION</td>
<td>“Maintenance of Catheter Patency” subsection, second paragraph</td>
<td>DELETED paragraph proposed in draft labeling submitted on 23-Dec-98:</td>
<td>This deletion, requested in the April 30, 1999 approvable letter, is ACCEPTABLE.</td>
</tr>
</tbody>
</table>

**S-033: “GERIATRIC USE” LABELING**

<table>
<thead>
<tr>
<th>Revised Section</th>
<th>Exact Location</th>
<th>Revised to:</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL PHARMACOLOGY</td>
<td>third, stand-alone, paragraph</td>
<td>“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.”</td>
<td>This revision, requested in the October 14, 1999 approvable letter, is ACCEPTABLE.</td>
</tr>
<tr>
<td>Revised Section</td>
<td>Exact Location</td>
<td>Revised to:</td>
<td>Recommendation</td>
</tr>
<tr>
<td>-----------------</td>
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<td>-------------</td>
<td>----------------</td>
</tr>
<tr>
<td>PRECAUTIONS</td>
<td>“General” subsection, “Increased Risk” sub-subsection</td>
<td>“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.”</td>
<td>This revision, requested in the October 14, 1999 approvable letter, is ACCEPTABLE.</td>
</tr>
<tr>
<td>PRECAUTIONS</td>
<td>“Geriatric Use” subsection</td>
<td>“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).”</td>
<td>This revision, requested in the October 14, 1999 approvable letter, is ACCEPTABLE.</td>
</tr>
</tbody>
</table>

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

/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
Dear Ms. Marconi:

We acknowledge receipt of your supplemental application for the following:

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

NDA Number: NDA 18-609

Supplement Number: S-035

Therapeutic Classification: Standard

Date of Supplement: July 8, 1999

Date of Receipt: July 9, 1999

This supplement proposes the following change: in the PRECAUTIONS section, the addition of a “Geriatric Use” subsection, 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 (vol. 62, No. 166, pages 45313-45326).

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 September 7, 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-035
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/J.Schmeling

DISTRICT OFFICE

Drafted by: KO/July 22 1999  K. Oliver  07/22/99
Final: KO/07/22/99/c:\data\mydocuments\NDA18609-07-22-99-S-035-ackger

SUPPLEMENT ACKNOWLEDGEMENT (AC)