



NDA 18388/S-084

**SUPPLEMENT APPROVAL**

Hospira, Inc.  
Attention: Linda Kapolnek  
Associate, Global Regulatory Affairs  
275 North Field Drive  
Dept. 0389, Building H2-2  
Lake Forest, IL 60045

Dear Ms. Kapolnek:

Please refer to your Supplemental New Drug Application (sNDA) dated July 15, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lidocaine Hydrochloride (4% and 8%) and Dextrose 5% Injection.

This “Changes Being Effected” supplemental new drug application provides for labeling revised as follows:

1. The CLINICAL PHARMACOLOGY section has been changed from:

[Redacted text] (b) (4)

[Redacted text]

[Redacted text]

[Redacted text] (b) (4)

[Redacted text]

(b) (4)

To:

Lidocaine hydrochloride exerts an antiarrhythmic effect by increasing the electric stimulation threshold of the ventricle during diastole. In usual therapeutic doses, lidocaine hydrochloride produces no change in myocardial contractility, in systemic arterial pressure, or in absolute refractory period.

About 90% of an administered dose of the drug is metabolized in the liver. The remaining 10% is excreted unchanged via the kidneys.

Lidocaine toxicity is related to systemic blood levels. The decreased clearance and longer half-life of lidocaine should be taken into consideration with prolonged (24 hour) infusions. Constant rate of infusion may result in toxic accumulation of lidocaine. Infusion should be reduced to approximately one-half to compensate for decreased rate of clearance and concomitant or prior administration of propranolol may further increase blood concentrations by as much as 30% in patients without cardiac or hepatic failure. In clinical studies, patients over 65 years showed decreased lidocaine clearance. This was partly due to the tendency of elderly patients to have lower body weight and the increased risk of cardiac failure in these patients.

This solution provides approximately 170 calories per liter.

2. The CONTRAINDICATIONS section has been changed from:

(b) (4)

To:

Lidocaine hydrochloride is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.

Lidocaine should not be used in patients with Stokes-Adams syndrome, Wolff-Parkinson-White Syndrome, or with severe degrees of sinoatrial, atrioventricular, or intraventricular block.

Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

3. The WARNINGS section has been changed from:

(b) (4)



(b) (4)



To:

Constant monitoring with an electrocardiograph is essential to the proper administration of lidocaine hydrochloride intravenously. Signs of excessive depression of cardiac conductivity, such as prolongation of the PR interval, widening of the QRS interval or appearance or aggravation of arrhythmias, should be followed by prompt cessation of the intravenous infusion of this agent. It is mandatory to have emergency resuscitative equipment and drugs immediately available to manage adverse reactions involving cardiovascular, respiratory, or central nervous systems. Occasional acceleration of ventricular rate may occur when lidocaine hydrochloride is administered to patients with atrial fibrillation. Evidence for proper usage in pediatric patients is limited. Anaphylactic reactions may occur following administration of lidocaine hydrochloride. In the case of severe reaction, discontinue the use of the drug.

Because dosages of this drug are titrated to response (see **DOSAGE AND ADMINISTRATION**), no additives should be made to Lidocaine Hydrochloride and 5% Dextrose Injection USP.

4. The PRECAUTIONS section has been changed from:

(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

To:

**General**

Caution should be employed in the repeated use of lidocaine hydrochloride in patients with severe liver or renal disease because accumulation may occur and lead to toxic phenomena, since lidocaine hydrochloride is metabolized mainly in the liver and excreted by the kidneys. The drug should also be used with caution in patients with hypovolemia and shock, and in all forms of heart block (see *CONTRAINDICATIONS* and *WARNINGS*).

In patients with sinus bradycardia or incomplete heart block, the administration of lidocaine hydrochloride intravenously for the elimination of ventricular ectopic beats without prior acceleration in heart rate (e.g., by isoproterenol or by electric pacing) may promote more frequent and serious ventricular arrhythmias or complete heart block (see *CONTRAINDICATIONS*).

Most potent anesthetic agents, local anesthetics of the amide type which includes lidocaine, and muscle relaxants of both depolarizing and nondepolarizing types have been associated with malignant hyperthermia.

Care should be taken in the administration of intravenous fluids in patients with compromised myocardial function to avoid fluid overload or disturbances of serum electrolyte concentrations which might interfere with cardiac conduction or result in congestive heart failure.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result. If administration is not controlled by a pumping device, refrain from applying excessive pressure (>300mmHg) causing distortion to the container such as wringing or twisting. Such handling could result in breakage of the container.

These solutions are intended for intravenous administration using sterile equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours.

Use only if solution is clear and container and seals are intact.

- 5. The Drug Interactions section has been revised to include potential interactions with cimetidine and amiodarone.
- 6. The following new section has been added:

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long term animal studies have not been performed to evaluate carcinogenic potential of lidocaine; nor have studies been conducted to assess the mutagenic potential of lidocaine or its potential to affect fertility.

- 7. The ADVERSE REACTIONS section has been changed from:

[Redacted text block containing multiple lines of obscured content, likely the original Adverse Reactions section. A small "(b) (4)" label is visible at the top right of the first redacted line.]

To:

Systemic reactions of the following types have been reported:

1. Central Nervous System: Light-headedness; drowsiness; dizziness; apprehension; euphoria; tinnitus; blurred or double vision; vomiting; sensation of heat, cold or numbness; twitching; tremors; convulsions; unconsciousness; respiratory depression and arrest.
  2. Cardiovascular System: Hypotension; cardiovascular arrest; and bradycardia which may lead to cardiac arrest.
  3. Hematologic Effects: methemoglobinemia.
  4. Allergic reactions, including anaphylactic reactions, may occur but are infrequent. There have been no reports of cross-sensitivity between lidocaine hydrochloride and procainamide or between lidocaine hydrochloride and quinidine.
8. The MANAGEMENT OF ADVERSE REACTIONS section has been deleted.
9. The OVERDOSAGE section has been changed from:

(b) (4)

To:

Overdosage results in systemic toxicity (see *ADVERSE REACTIONS*).

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Amundson Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, Pharm.D.  
Deputy Director for Safety  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
01/15/2014