DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 018461/S-058

SUPPLEMENT APPROVAL

Baxter Healthcare Corporation
Attention: Jodie Stennett
Senior Associate, Regulatory Affairs
32650 N. Wilson Road
Mail Stop WG1-3
Round Lake IL 60073

Dear Ms. Stennett:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 20, 2016, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lidocaine Hydrochloride and 5% Dextrose for Injection.

We also refer to your amendment dated August 18, 2016.

This supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

1. The **CLINICAL PHARMACOLOGY** section was revised to read:

Mechanism of Action

Lidocaine hydrochloride exerts an antiarrhythmic effect by increasing the electrical 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.

(b) (4)

Central nervous system adverse reactions become apparent with increasing venous plasma levels above 6.0 µg free base per mL. (b) (4)

Pharmacokinetics

The plasma protein binding of lidocaine (b) (4) is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 micrograms of free base per milliliter 60 to 80 percent of lidocaine (b) (4) is protein bound. Binding is also dependent on the plasma concentration of alpha-1-acid glycoprotein.

Lidocaine (b) (4) crosses the blood-brain and placental barriers, presumably by passive diffusion.

Approximately 90% of lidocaine [(b) (4)] administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. ~~About 90% of an administered dose of the drug is metabolized in the liver. The remaining 10% is excreted unchanged via the kidneys.~~ Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. CYP1A2 and CYP3A4 mediated N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX). The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine [(b) (4)] The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline. The elimination half-life of lidocaine [(b) (4)] following an intravenous bolus injection is typically 1.5 to 2.0 hours.

Specific Populations

Hepatic Impairment

Because of the rapid rate at which lidocaine [(b) (4)] is metabolized, any condition that affects liver function may alter lidocaine [(b) (4)] kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. [(b) (4)]

Renal Impairment

Mild or moderate renal [(b) (4)] impairment does not affect lidocaine kinetics; while in patients with severe renal dysfunction, lidocaine clearance is decreased by [(b) (4)] half and the accumulation of GX increased by [(b) (4)] 1.5-fold.

~~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 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% (See Drug Interactions).~~

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.

2. The **CONTRAINDICATIONS** section was revised to read:

Contraindications

Hypersensitivity reactions, including anaphylactic reactions, have been reported with lidocaine. Lidocaine hydrochloride is contraindicated in patients with a history of hypersensitivity to local anesthetics of the amide type.

Lidocaine ~~should not be used~~is contraindicated 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 was revised to read:

Constant monitoring with an electrocardiograph is essential to the administration of lidocaine hydrochloride intravenously. Signs of excessive depression of cardiac conductivity, such as prolongation of the PR interval, widening of the QRS interval and the 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. Central nervous system adverse reactions are associated with venous plasma levels above 6.0 μg free base per mL (see ADVERSE REACTIONS).

Hypersensitivity, including anaphylaxis, has been reported with lidocaine-containing solutions. Stop the infusion immediately if signs of hypersensitivity develop.

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).

~~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 and the 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.~~

Because lidocaine is metabolized mainly in the liver and excreted by the kidneys,~~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.~~ patients with renal or hepatic insufficiency may be at increased risk for toxicity.

~~Occasional acceleration of ventricular rate may occur when lidocaine hydrochloride is administered to patients with atrial fibrillation. Evidence for proper usage in children is limited.~~

~~Anaphylactic reactions may occur following administration of lidocaine hydrochloride. (See **ADVERSE REACTIONS**).~~

~~In the case of severe reaction, discontinue the use of the drug.~~

~~Administer Lidocaine Hydrochloride and 5% Dextrose Injection, USP only with a calibrated infusion device.~~

4. Under **PRECAUTIONS**,**General** the following text was added/deleted:

~~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 non-depolarizing types, have been associated with malignant hyperthermia.~~

If malignant hyperthermia develops, discontinue administration immediately and institute therapeutic countermeasures as clinically indicated.

~~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.~~

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

Lidocaine hydrochloride should not be added to blood transfusion assemblies because of the possibilities of pseudoagglutination or hemolysis.

5. The **PRECAUTIONS**, **Drug Interactions** section was revised to read:

~~Pharmacodynamic Interactions~~

Digitalis derivatives: Monitor toxicity when lidocaine ~~should be~~is used ~~with caution~~ in patients with digitalis toxicity accompanied by supraventricular arrhythmia and/or atrioventricular block (see **Contraindications**).

(b) (4)

When lidocaine is administered with other antiarrhythmic drugs such as amiodarone, phenytoin, procainamide, propranolol or quinidine, the cardiac effects may be additive or antagonistic and toxic effects may be additive. ~~**Phenytoin may stimulate the hepatic metabolism of lidocaine, but the clinical significance of this effect is not known.**~~

(b) (4)

Coadministration of propranolol or cimetidine with lidocaine has been reported to reduce the clearance of lidocaine from the plasma and may result in toxic accumulation of the drug.

(b) (4)

Pharmacokinetic Interactions

Concomitant treatment with (b) (4) drugs which are inhibitors of CYP1A2 and/or CYP3A4 has the potential to increase lidocaine plasma levels (b) (4) by decreasing lidocaine clearance and thereby prolonging the elimination half-life. Monitor toxicity when administering lidocaine with CYP1A2 and/or CYP3A4 inhibitors.

Concomitant use of lidocaine at steady-state concentrations of the CYP1A2 inhibitor fluvoxamine increases intravenous lidocaine plasma AUC and Cmax by 71% and 22%, and decreases MEGX AUC and Cmax by 54% and 65%. Fluvoxamine decreases the plasma clearance of lidocaine by 41%-60% and prolonged the mean half-life one hour. Monitor toxicity when coadministering these medications.

(b) (4) Concomitant use of lidocaine with propofol, a hypnotic agent and CYP3A4 inhibitor, may increase lidocaine plasma levels by reducing lidocaine clearance. (b) (4) Monitor toxicity when coadministering lidocaine with propofol.

(b) (4)

Concomitant treatment with drugs which are inducers of CYP1A2 and/or CYP3A4 (e.g., phenytoin) has the potential to decrease lidocaine plasma levels and higher doses may be required.

Concomitant use of lidocaine with a weak CYP1A2 and CYP3A4 inhibitor has been reported to increase lidocaine plasma levels by 24% – 75% and may result in toxic accumulation of the drug. Monitor toxicity when coadministering lidocaine with cimetidine.

Beta-adrenergic blockers (e.g. propranolol): Concomitant use of lidocaine with beta-adrenergic blockers may increase lidocaine plasma levels by decreasing hepatic blood flow and thereby decrease lidocaine clearance. Monitor for toxicity when coadministering lidocaine with drugs that decrease hepatic blood flow.

(b) (4)

~~When lidocaine is administered with other antiarrhythmic drugs such as amiodarone, phenytoin, procainamide, propranolol or quinidine, the cardiac effects may be additive or antagonistic and toxic effects may be additive. Phenytoin may stimulate the hepatic metabolism of lidocaine, but the clinical significance of this effect is not known.~~

(b) (4)

6. Under **PRECAUTIONS,Pregnancy**, the following text was added/deleted:

Teratogenic Effects: ~~**Pregnancy Category B**~~
Reproduction studies have been performed in rats at doses up to five times the maximum human dose and have revealed no significant findings. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, physicians should carefully consider the potential risks and benefits for each specific patient before prescribing lidocaine hydrochloride. ~~**should be used during pregnancy only if clearly needed.**~~

Lidocaine may cross the placental barrier.

7. Under **PRECAUTIONS,Nursing Mothers**, the following text was added/deleted:

Lidocaine is present in human milk. Published studies have reported a range of lidocaine milk: plasma ratios between 0.4-1.1. Limited data available on lidocaine's effects on the breastfed child have not revealed a consistent pattern of associated adverse events. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for lidocaine and any potential adverse effects on the breastfed infant from lidocaine or from the underlying maternal condition. (b) (4)
~~**. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine hydrochloride is administered to a nursing woman.**~~

8. Under **Adverse Reactions**, the following text was added/deleted:

Nervous System Disorders~~Central Nervous System~~: respiratory depression and arrest; unconsciousness; convulsions; tremors; twitching; vomiting; blurred or double vision; drowsiness; dizziness; light-headedness; tinnitus; sensation of heat, cold or numbness; euphoria; apprehension; agitation; confusional state; paresthesia; dysarthria.

Cardiovascular System: cardiovascular arrest; bradycardia which may lead to cardiac arrest; hypotension, Ventricular fibrillation, Ventricular tachycardia, Ventricular arrhythmia, Asystole.

Gastrointestinal Disorders: Hypoesthesia oral, Nausea,

Hematologic Effects: methemoglobinemia.

Psychiatric Disorders: Disorientation

9. Under **Overdosage**, the following text was added:

Signs and symptoms of overdose may include:

- Central nervous system effects, e.g., coma, loss of consciousness, CNS depression, seizure, tonic-clonic muscle jerks, tremor, nystagmus, tingling of tongue and lips, tinnitus, drowsiness, disorientation, and lightheadedness.

- Cardiorespiratory effects, e.g., cardiovascular collapse and cardiorespiratory arrest (sometimes fatal), respiratory depression and arrest, hypotension, myocardial depression, arrhythmias, including asystole, heart block, ventricular arrhythmias, tachycardia, and bradycardia.

Discontinue lidocaine administration in the event of an overdose.

There is no specific antidote for overdose of lidocaine. The risk of overdose can be minimized by close monitoring during treatment.

Emergency procedures should include appropriate corrective, resuscitative, and other supportive measures (See Warnings).

~~Overdosage may result in severe systemic toxicity (see **Warnings and Precautions** and **Adverse Reactions**).~~

10. Under **Dosage and Administration**, the following text was added/deleted to/from the first, third, fifth, and 6th paragraphs:

Therapy of ventricular arrhythmias is often initiated with a single IV bolus of 1.0 to 1.5 mg/kg at a rate of 25 to 50 mg/min.~~50 to 100 mg~~ of lidocaine hydrochloride injection. Following acute treatment by bolus in patients in whom arrhythmias tend to recur and who are incapable of receiving oral antiarrhythmic agents, intravenous infusion of Lidocaine Hydrochloride and 5% Dextrose Injection, USP is administered continuously at the rate of 1 to 4 mg/min (0.020 to 0.050 mg/kg/min~~20 to 50 mcg/kg/min~~ in the average 70 kg adult). The 0.4% solution (4 mg/mL) can be given at a rate of 15 to 60 mL/hr (0.25 to 1 mL/min). The 0.8% solution (8 mg/mL) can be given at a rate of 7.5 to 30 mL/hr (0.12 to 0.5 mL/min). Precise dose~~age regimen~~ is determined by patient characteristics and response.

~~Pharmacokinetic data indicate reduced elimination of lidocaine after prolonged infusion (24 hours)~~Infusion rate should be reduced by approximately one-half to compensate for decreased rate of clearance after prolonged infusion (24 hours) (see **Clinical Pharmacology**). ~~and concomitant or prior administration of propranolol may further increase blood concentrations by as much as 30% with resultant prolongation of the half-life to approximately three times that seen following a single administration~~. Failure to adjust the rate of infusion in keeping with this altered ability to eliminate lidocaine may result in toxic accumulation of the drug in the patient's serum.

Intravenous infusions of lidocaine hydrochloride must be administered under constant ECG monitoring to avoid potential overdosage and toxicity. Intravenous infusion should be terminated as soon as the patient's basic cardiac rhythm appears to be stable or at the

earliest signs of toxicity (see OVERDOSAGE). It should rarely be necessary to continue intravenous infusions beyond 24 hours. As soon as possible and when indicated, patients should be changed to an oral antiarrhythmic agent for maintenance therapy.

Pediatric: ~~Although controlled c~~Clinical studies to establish pediatric dosing schedules have not been conducted~~, the American Heart Association's Standards and Guidelines recommends a bolus dose of 1 mg/kg followed by an infusion rate of 30 µg/kg/min~~ (b) (4) 20 to (b) (4) 50 mg/kg/min). The bolus dose should be repeated if infusion is not initiated within 15 minutes of the initial bolus dose.

Hepatic Impairment: (b) (4) ~~is~~ likely to decrease clearance and increase exposure level of lidocaine. Administer lidocaine at a lower maintenance infusion rate with close ~~toxicity~~ monitoring of toxicity in patients with hepatic impairment.

Renal Impairment: In patients with severe renal impairment (creatinine clearanceeGFR less than 30 mL/min/1.73 m2), administer lidocaine at lower maintenance infusion rate with close ~~toxicity~~ monitoring of toxicity.

Drug Interactions:
~~Concomitant treatment with drugs which are inhibitors of CYP1A2 and/or CYP3A4 has the potential to increase lidocaine plasma levels and by decreasing lidocaine clearance and thereby prolonging the elimination half life. Monitor toxicity when administering lidocaine with CYP1A2 and/or CYP3A4 inhibitors.~~

~~Lidocaine hydrochloride should not be added to blood transfusion assemblies.~~

Lidocaine is incompatible with the following due to precipitate formation (includes but is not limited to):

- Amphotericin
- Cephazolin sodium
- Phenytoin sodium

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless solution is clear and seal is intact. Use of a final filter is recommended during administration of all parenteral solutions, where possible. Lidocaine must not be infused simultaneously through the same tubing with other medicinal products without first verifying their compatibility.

11. The following section was deleted:

~~**Directions for Use of VIAFLEX Plus Plastic Container:**~~

(b) (4)

~~**Caution:** 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.~~

(b) (4)

~~**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 protector from administration port at bottom of container.~~
~~3. Attach administration set. Refer to complete directions accompanying set.~~

12. The revision date was updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, as amended, and 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), 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 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).

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
02/07/2017