DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020201/S-036

SUPPLEMENT APPROVAL

Hospira, Inc.
Attention: Ms. Laura Kapolnek
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045

Dear Ms. Kapolnek:

Please refer to your Supplemental New Drug Application (sNDA) dated November 13, 2013, received November 13, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dobutamine in 5% Dextrose Injection, USP in Flexible Plastic Containers.

This Prior Approval supplemental new drug application provides for updates to the package insert. In addition, annual-reportable changes and minor editorial/formatting corrections were made throughout the labeling since the last approved labeling (S-013, approved April 10, 2001). The changes are listed below as follows (additions are shown as underlined text and deletions are shown as ~~strike-through text~~):

1. The terms "Rx only" has been added following the drug name.

2. The term "USP" has been added following "Dobutamine in 5% Dextrose Injection" in various places throughout the labeling.

3. Under **DESCRIPTION**, the first sentence of the second paragraph has been changed as follows:

   Each 100 mL contains dobutamine hydrochloride equivalent to (b) (4) 100 mg, 200 mg, or 400 mg of dobutamine; dextrose (derived from corn), hydrous 5 g in water for injection, with sodium metabisulfite 25 mg and edetate disodium, dihydrate 10 mg added as stabilizers; osmolar concentration, respectively, (b) (4) ~~,~~ 263, 270, or 284 mOsmol/liter (calc.).

4. Under **INDICATIONS AND USAGE**, the term "patients with" has been added in the first sentence as follows:

   Dobutamine in 5% Dextrose Injection, USP is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of patients with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

5. Under **CONTRAINDICATIONS**, the following changes were made:

   Dobutamine in 5% Dextrose Injection, USP is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to dobutamine or any of its components.

(b) (4)

6. Under **WARNINGS**, the following changes were made:

   a. The 1-4 numbering of each subsection has been deleted.
   b. Under the "**Increase in Heart Rate or Blood Pressure**" subsection, the third sentence has been changed as follows: "Usually, reduction of dosage- (b) (4) reverses these effects."
   c. Under the "**Hypersensitivity**" subsection, the following sentence has been deleted: (b) (4)

7. Under **PRECAUTIONS**, the following changes were made:

   a. The term "**General**" has been added and the numbering 1-8 has been deleted.
   b. The following sentence has been bolded: "**During the administration of dobutamine, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutamine in 5% Dextrose Injection, USP.**"
   c. The following changes were made:

(b) (4)

(b) (4)-Do not administer unless solution is clear and container is undamaged. Discard unused portion.

d. Under the **Geriatric Use** subsection, the following changes were made:

Geriatric Use: Clinical studies of dobutamine did not include sufficient numbers of subjects aged 65 and over (b) (4) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients (b) (4) In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater

frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or (b) (4) drug therapy.

8. Under **ADVERSE REACTIONS**, the following changes were made:

   a. In the **Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity** subsection:

      A 10- to 20-mm Hg increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/minute have been noted in most patients (see **WARNINGS** regarding exaggerated chronotropic and pressor effects). Approximately 5% of adult patients have had increased premature ventricular beats during infusions. These effects are dose related.

   b. In the **Miscellaneous Uncommon Effects** subsection:

      The following adverse effects have been reported in 1% to 3% of adult patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

      Administration of dobutamine, like other catecholamines, has been associated with decreases in serum potassium concentrations, rarely to hypokalemic (b) (4) values (See PRECAUTIONS).

9. Under **DOSAGE AND ADMINISTRATION**, the entire text and Dobutamine Infusion Rate (mL/hr) Charts have been replaced with the following:

   Recommended Dosage
   Dobutamine in 5% Dextrose Injection, USP is administered intravenously through a suitable intravenous catheter or needle. A calibrated electronic infusion device is recommended for controlling the rate of flow in mL/hour or drops/minute.

   Infusion of dobutamine should be started at a low rate (0.5-1.0 µg/kg/min) and titrated at intervals of a few minutes, guided by the patient's response, including systemic blood pressure, urine flow, frequency of ectopic activity, heart rate, and (whenever possible) measurements of cardiac output, central venous pressure, and/or pulmonary capillary wedge pressure. In reported trials, the optimal infusion rates have varied from patient to patient, usually 2-20 µg/kg/min but sometimes slightly outside of this range. On rare occasions, infusion rates up to 40 µg/kg/min have been required to obtain the desired effect.

   Rates of infusion in mL/hour for dobutamine hydrochloride concentrations of 500, 1,000, 2,000 and 4,000 mg/L may be calculated using the following formula:

   $$\textbf{Infusion Rate (mL/h)} = \frac{\textbf{[Dose (µg/kg/min) x Weight (kg) x 60 min/h]}}{\textbf{Final Concentration (µg/mL)}}$$

   Example calculations for infusion rates are as follows:

   Example 1: for a 60 kg person at an initial dose of 0.5 µg/kg/min using a 500 µg/mL concentration, the infusion rate would be as follows:

   $$\textbf{Infusion Rate}\ (\text{mL/h}) = \frac{[\textbf{0.5}\ (\mu\text{g/kg/min}) \times \textbf{60}\ (\text{kg}) \times \textbf{60}\ (\text{min/h})]}{\textbf{500}\ (\mu\text{g/mL})} = \textbf{3.6}\ (\text{mL/h})$$

Example 2: for a 80 kg person at a dose of 10 µg/kg/min using a 2,000 µg/mL concentration, the infusion rate would be as follows:

$$\textbf{Infusion Rate}\ (\text{mL/h}) = \frac{[\textbf{10}\ (\mu\text{g/kg/min}) \times \textbf{80}\ (\text{kg}) \times \textbf{60}\ (\text{min/h})]}{\textbf{2,000}\ (\mu\text{g/mL})} = \textbf{24}\ (\text{mL/h})$$

This container system may be inappropriate for the dosage requirements of pediatric patients under 30 kg.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Dobutamine in 5% Dextrose Injection, USP solutions may exhibit a pink color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency.

Solutions containing dextrose should not be administered through the same administration set as blood, as this may result in pseudoagglutination or hemolysis.

Do not add supplementary medications to Dobutamine in 5% Dextrose Injection, USP. Do not administer Dobutamine in 5% Dextrose Injection, USP simultaneously with solutions containing sodium bicarbonate or strong alkaline solutions.

10. Under **HOW SUPPLIED**, the following changes were made:

(b) (4)

-Do not freeze. Store at 20 to 25ºC (68 to 77ºF). [See USP Controlled Room Temperature.] (b) (4)

There were no other changes when compared with the last approved labeling supplement (S-013, approved April 10, 2001).

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 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).

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 contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

NORMAN L STOCKBRIDGE
05/31/2016