DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19970/S-018

SUPPLEMENT APPROVAL

Baxter Healthcare Corporation
Attention: Jodie Stennett
Senior Associate, Regulatory Affairs
32650 N. Wilson Road, Mail Stop WG2-3S
Round Lake, IL 60073

Dear Ms. Stennett:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 22, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nitroglycerin in 5% Dextrose for Injection.

This Prior Approval supplemental new drug application provides for the following changes to labeling:

1. Under **DESCRIPTION**, the following statement was added after the second paragraph:

   Dextrose is derived from corn.

2. Under **INDICATIONS AND USAGE**, the word "congestive" was deleted from the first paragraph.

3. Under **CONTRAINDICATIONS**, the following text was added as the fifth and sixth paragraphs:

   Nitroglycerin is contraindicated in patients with uncorrected hypovolemia.

   Nitroglycerin is also contraindicated in patients with increased intracranial pressure.

4. Under **WARNINGS**, the following text was added to the section:

   Use of PVC (polyvinyl chloride) tubing in infusion sets may lead to loss of active ingredient due to adsorption of nitroglycerin to PVC tubing, therefore dosage is affected (see **Dosage and Administration**). Nitroglycerin adsorption by PVC tubing is increased when the tubing is long, the flow rates are low, and the nitroglycerin concentration of the solution is high. The delivered fraction of the solution's original nitroglycerin content has been 20-60% in published studies

using PVC tubing; the fraction varies with time during a single infusion, and no simple correction factor can be used. PVC tubing has been used in most published studies of intravenous nitroglycerin, but the reported doses have been calculated by simply multiplying the flow rate of the solution by the solution's original concentration of nitroglycerin. **The actual doses delivered have been less, sometimes much less, than those reported.**
Relatively non-ad~~b~~sorptive intravenous administration sets are available. **If intravenous nitroglycerin is administered through non-ad~~b~~sorptive tubing, doses based upon published reports will generally be too high.**

Some in-line intravenous filters also ad~~b~~sorb nitroglycerin; these filters should be avoided.

Solutions containing dextrose without electrolytes should not be administered through the same administration set as blood, as this may result in pseudoagglutination or hemolysis.

The intravenous administration of solutions may cause fluid overloading resulting in dilution of serum electrolyte concentrations, overhydration and congested states of 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 concentration of the injections.

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

~~General~~: Severe hypotension and shock may occur with even small doses of nitroglycerin. ~~This drug should therefore be used with caution in~~Monitor patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Tolerance development and occurrence of cross tolerance to other nitro compounds have been reported.

In industrial workers who have long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Some clinical trials in angina patients have provided nitroglycerin for about 12 continuous hours of every 24-hour day. During the nitrate-free intervals in some

of these trials, anginal attacks have been more easily provoked than before treatment, and patients have demonstrated hemodynamic rebound and decreased exercise tolerance. The importance of these observations to the routine, clinical use of intravenous nitroglycerin is not known.

Lower concentrations of Nitroglycerin in 5% Dextrose Injection increase the potential precision of dosing, but these concentrations increase the total fluid volume that must be delivered to the patient. Total fluid load may be a dominant consideration in patients with compromised function of the heart, liver, and/or kidneys.

Administer ~~N~~nitroglycerin in 5% Dextrose Injection ~~should be administered~~ only via an infusion pump that can maintain a constant infusion rate.

Intracoronary injection of Nitroglycerin in 5% Dextrose Injection has not been studied.

Monitor patients with known sub-clinical or overt diabetes mellitus when using solutions containing dextrose.~~Solutions containing dextrose should be used with caution in patients with known sub-clinical or overt diabetes mellitus.~~

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

Drug Interactions: The vasodilating effects of nitroglycerin may be additive with those of other ~~vasodilators~~ antihypertensives. (e.g., beta-blockers, calcium channel blockers and tricyclic antidepressants) and may cause increased hypotensive effects.

Concomitant use of Nitroglycerin in 5% Dextrose Injection c~~C~~oncomitant use ~~of Nitroglycerin in 5% Dextrose Injection~~ with phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, or vardenafil) in any form is contraindicated (see **Contraindications**).

Concomitant use of Nitroglycerin in 5% Dextrose Injection with riociguat, a soluble guanylate cyclase stimulator, can cause hypotension and is contraindicated (see **Contraindications)**.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination.

~~Intravenous nitroglycerin interferes, at least in some patients, with the anticoagulant effect of heparin. In patients receiving intravenous nitroglycerin, concomitant heparin therapy should be guided by frequent measurement of the activated partial thromboplastin time.~~
Nitroglycerin at higher dosages may interfere with the anticoagulant effect of heparin. Intravenous nitroglycerin can induce heparin resistance.

Administration of Nitroglycerin in 5% Dextrose Injection through the same infusion set as blood can result in pseudoagglutination and hemolysis. ~~More generally,~~ Do not mix Nitroglycerin in 5% Dextrose Injection ~~should not be mixed~~ with any other medication of any kind.

7. The Pregnancy category "C" was removed.

8. **PRECAUTIONS, Nursing Mothers**, the following was added/deleted from the section:

It is not known if nitroglycerin is present in human milk or if nitroglycerin has effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for nitroglycerin and any potential adverse effects on the breastfed child from nitroglycerin or from the underlying maternal condition.
~~It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for adverse reactions in nursing infants from Nitroglycerin in 5% Dextrose Injection, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.caution should be exercised when nitroglycerin is administered to a nursing woman.~~

9. Under **PRECAUTIONS,Pediatric Use**, the following text was added/deleted from the section:

Safety and effectiveness in the pediatric population have not been established. However, the relationship between hemodynamic effects of nitroglycerin and dose in the pediatric population have been documented in the literature. Studies in the literature used doses of nitroglycerin injection in pediatric patients ranging from 0.5 to 5 mcg/kg/min. The following equation can be used to calculate the flow rate in mL/hour of nitroglycerin using the 100 mcg/mL (25 mg/250 mL) concentration of nitroglycerin.

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

Example calculations for infusion rates are as follows:

Example 1: for a 2 kg child at a dose of 0.5 µg/kg/min using a 100 mcg/mL concentration, the infusion rate would be as follows:

$$\textbf{Infusion Rate} \text{ (mL/h)} = \frac{[0.5 \text{ (mcg/kg/min)} \times 2 \text{ (kg)} \times 60 \text{ (min/h)}]}{100 \text{ (mcg/mL)}} = 0.6 \text{ (mL/h)}$$

Example 2: for a 10 kg child at a dose of 5 mcg/kg/min using a 100 mcg/mL concentration, the infusion rate would be as follows:

$$\textbf{Infusion Rate}\ (\text{mL/h}) = \frac{[5\ (\text{mcg/kg/min}) \times 10\ (\text{kg}) \times 60\ (\text{min/h})]}{100\ (\text{mcg/mL})} = 30\ (\text{mL/h})$$

Note: Very low infusion rates may require that a more dilute concentration of nitroglycerin infusion solution be prepared.

~~Table 2~~

~~Studies in the literature used doses of nitroglycerin injection in pediatric patients ranging from 0.5 to 5 mcg/kg/min. The following chart can be used to calculate the flow rate in mL/hour of nitroglycerin using the 100 mcg/mL (25 mg/250 mL) concentration of nitroglycerin.~~

~~Note: Very low infusion rates may require that a more dilute concentration of nitroglycerin infusion solution be prepared.~~

~~Flow Rate (mL/hour)~~

~~Using the 100 mcg/mL (25mg/250 mL) Concentration~~

~~Dose (mcg/kg/min) — Patient Weight in kg~~

	2	4	6	8	10	12	14	16	18	20
0.1*	0.12	0.24	0.36	0.48	0.6	0.72	0.84	0.96	1.08	1.2
0.5	0.6	1.2	1.8	2.4	3	3.6	4.2	4.8	5.4	6
1	1.2	2.4	3.6	4.8	6	7.2	8.4	9.6	10.8	12
2	2.4	4.8	7.2	9.6	12	14.4	16.8	19.2	21.6	24
3	3.6	7.2	10.8	14.4	18	21.6	25.2	28.8	32.4	36
4	4.8	9.6	14.4	19.2	24	28.8	33.2	38.4	43.2	48
5	6	12	18	24	30	36	42	48	54	60
10*	12	24	36	48	60	72	84	96	108	120

~~*Dose not studied in pediatric trials~~

10. Under **PRECAUTIONS, Adverse Reactions**, the following text was added as the fourth paragraph:

Dyspnea has also been reported.

11. Under **PRECAUTIONS, Overdosage**, the following text was added:

Signs and symptoms of overdose are generally similar to the described adverse reactions (see **Adverse Reactions**).

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

12. Under **PRECAUTIONS, Methemoglobinemia**, the following text was added/deleted:

Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant (10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

~~Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.~~ Cases of methemoglobuilinemia have been reported with moderate doses of organic nitrates.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

~~When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.~~

When methemoglobinemia is diagnosed, discontinue treatment of nitroglycerin. If condition is not reversed, treat with methylene blue, 1-2 mg/kg intravenously.

13. Under **DOSAGE AND ADMINISTRATION**, the following text was added/deleted:

Nitroglycerin in 5% Dextrose Injection is intended for intravenous administration using sterile equipment. ~~It should be a~~Administer~~ed~~ Nitroglycerin in 5% Dextrose Injection only via an infusion pump that can maintain a constant

infusion rate. Do not use a~~A~~ container which has lost its vacuum, or one in which particulate matter is visible~~, should not be used~~.

Dosage is affected by the type of infusion set used (see **Warnings**). Although the usual adult starting dose in published studies has been 25 mcg/min or more, these studies used PVC tubing, so the delivered doses were less than those reported. **When nonad~~b~~sorptive tubing is used, doses must be reduced** (see **Warnings** and **Precautions)**.

The dosage must be determined by the patient's individual requirement and depending on the required response and possible adverse effects (see **Adverse Reactions**).

Even using nonadbsorptive tubing, the dose necessary to achieve a given response will vary greatly from patient to patient. Patients with normal or low left-ventricular filling pressure (e.g., patients with uncomplicated angina pectoris) may respond fully to as little as 5 mcg/min, while other patients may require a dose that is one or even two orders of magnitude higher. Continuous monitoring of blood pressure and heart rate is necessary in all patients receiving this medication; in many cases, invasive monitoring of pulmonary capillary wedge pressure will also be indicated.

Lower concentrations of Nitroglycerin in 5% Dextrose Injection increase the potential precision of dosing, but these concentrations increase the total fluid volume that must be delivered to the patient. Total fluid load may be a dominant consideration in patients with compromised function of the heart, liver, and/or kidneys. The necessary flow rates to achieve various dose rates with the available concentrations are shown in the following table.

Using nonadbsorptive tubing, the initial adult dosage of Nitroglycerin in 5% Dextrose Injection should be 5 mcg/min. Subsequent titration must be guided by the clinical results, with dose increments becoming more cautious as partial response is seen. Initial titration should be in 5 mcg/min increments at intervals of 3 to 5 minutes. If no response is seen at 20 mcg/min, increments of 10 and even 20 mcg/min can be used. Once some hemodynamic response is observed, dosage increments should be smaller and less frequent.

When the concentration is changed, the tubing must be disconnected from the patient and flushed with the new solution before therapy is continued. If this precaution is not taken, then depending upon the tubing, pump, and flow rate used, it might be several hours before nitroglycerin is delivered at the desired rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact.

Do not add supplementary medication to Nitroglycerin in 5% Dextrose Injection.

Infusion Rate (mL/h) = [Dose (mcg/min) x 60 min/h]
Concentration (mcg/mL)

Example calculations for infusion rates are as follows:

Example 1: for a dose of 30 µg/min using a 100 mcg/mL concentration, the infusion rate would be as follows:

Infusion Rate (mL/h) = [30 (mcg/min) x 60 (min/h)] = 18 (mL/h)
100 (mcg/mL)

Example 2: for a dose of 240 mcg/min using a 400 mcg/mL concentration, the infusion rate would be as follows:

Infusion Rate (mL/h) = [5 (mcg/min) x 60 (min/h)] = 36 (mL/h)
400 (mcg/mL)

~~Table 3~~
~~Necessary Flow Rates (mL/hr*)~~

~~Desired Dose (mcg/min)~~	~~Solution Concentration (mcg/mL)~~		
	~~100~~	~~200~~	~~400~~
~~5~~	~~3~~	~~1.5~~	~~0.8~~
~~10~~	~~6~~	~~3.0~~	~~1.5~~
~~15~~	~~9~~	~~4.5~~	~~2.3~~
~~20~~	~~12~~	~~6~~	~~3~~
~~30~~	~~18~~	~~9~~	~~4.5~~
~~40~~	~~24~~	~~12~~	~~6~~
~~50~~	~~30~~	~~15~~	~~7.5~~
~~60~~	~~36~~	~~18~~	~~9~~
~~80~~	~~48~~	~~24~~	~~12~~

~~100 60 30 15~~
~~120 72 36 18~~
~~140 84 42 21~~
~~160 96 48 24~~
~~180 108 54 27~~
~~200 120 60 30~~
~~240 144 72 36~~
~~280 168 84 42~~
~~320 192 96 48~~
~~500 300 150 75~~

~~*With a set that produces 60 drops/mL, 1mL/hr = 1 drop/min.~~

14. Under **How Supplied**, the following text was added to the last paragraph:

    Discard any unused portion.

15. The word absorption was changed to adsorption in various sections throughout the label.

16. The revision date and version number was updated.

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

APPROVAL & LABELING

We have completed our review of this supplemental application 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, 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 include 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

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, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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, RAC
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 I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

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
08/22/2016