

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**14-879 / S-044**

***Trade Name:*** Baxter Healthcare Corporation

***Generic Name:*** (doxapram hydrochloride injection, USP)

***Sponsor:*** Baxter Healthcare Corporation

***Approval Date:*** March 17, 2005

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**14-879 / S-044**

## CONTENTS

### **Reviews / Information Included in this NDA Review.**

<b>Approval Letter</b>	<b>X</b>
<b>Not Approvable Letter(s)</b>	
<b>Final Printed Labeling</b>	<b>X</b>
<b>Medical Review(s)</b>	
<b>Chemistry Review(s)</b>	
<b>EA/FONSI</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology Review(s)</b>	
<b>Clinical Pharmacology/ Biopharmaceutics Review(s)</b>	
<b>Administrative and Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**14-879 / S-044**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 14-879/S-044

Baxter Healthcare Corporation  
Route 120 and Wilson Road  
RLT-10  
Round Lake, IL 60073-0490

Attention: Laura Cooper  
Manager, Drug Regulatory Affairs

Dear Ms. Cooper:

Please refer to your supplemental new drug application dated September 16, 2004, received September 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dopram Injection (doxapram hydrochloride injection, USP).

We acknowledge receipt of your submission dated December 22, 2004.

This "Changes Being Effected" supplemental new drug application provides removal of latex warning statements throughout the package inserts and components.

We have completed our review of this supplemental new drug application, as amended, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the labeling submitted on December 22, 2004.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 14-879/S-044.**" Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

NDA 14-879/S-044

Page 2

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, call Alison Meyer, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Division Director  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
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/

-----  
Bob Rappaport  
3/17/05 02:54:30 PM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**14-879 / S-044**

**APPROVED LABELING**

## DOPRAM Injection

(doxapram hydrochloride injection, USP)

**NOT FOR USE IN NEONATES**  
**CONTAINS BENZYL ALCOHOL**

R<sub>x</sub> only

### DESCRIPTION

DOPRAM Injection (doxapram hydrochloride injection, USP) is a clear, colorless, sterile, non-pyrogenic, aqueous solution with pH 3.5 to 5, for intravenous administration.

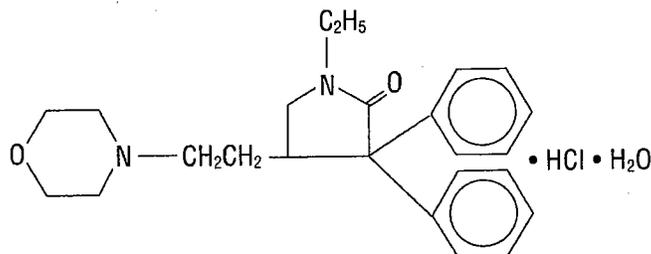
Each 1 mL contains:

Doxapram Hydrochloride, USP ..... 20 mg  
Benzyl Alcohol, NF (as preservative) ..... 0.9%  
Water for Injection, USP ..... q.s.

Doxapram Injection is a respiratory stimulant.

Doxapram hydrochloride is a white to off-white, crystalline powder, sparingly soluble in water, alcohol and chloroform. Chemically, doxapram hydrochloride is 1-ethyl-4-[2-(4-morpholinyl)ethyl]-3,3-diphenyl-2-pyrrolidinone monohydrochloride, monohydrate.

The chemical structure is:



$C_{24}H_{31}ClN_2O_2 \cdot H_2O$

M.W. 432.99

### CLINICAL PHARMACOLOGY

Doxapram hydrochloride produces respiratory stimulation mediated through the peripheral carotid chemoreceptors. As the dosage level is increased, the central respiratory centers in the medulla are stimulated with progressive stimulation of other parts of the brain and spinal cord.

The onset of respiratory stimulation following the recommended single intravenous injection of doxapram hydrochloride usually occurs in 20 to 40 seconds with peak effect at 1 to 2 minutes. The duration of effect may vary from 5 to 12 minutes.

The respiratory stimulant action is manifested by an increase in tidal volume associated with a slight increase in respiratory rate.

A pressor response may result following doxapram administration. Provided there is no impairment of cardiac function, the pressor effect is more marked in hypovolemic than in normovolemic states. The pressor response is due to the improved cardiac output rather than peripheral vasoconstriction. Following doxapram administration, an increased release of catecholamines has been noted.

Although opiate-induced respiratory depression is antagonized by doxapram, the analgesic effect is not affected.

## **INDICATIONS AND USAGE**

### **Postanesthesia**

- a. When the possibility of airway obstruction and/or hypoxia have been eliminated, doxapram may be used to stimulate respiration in patients with drug-induced postanesthesia respiratory depression or apnea other than that due to muscle relaxant drugs.
- b. To pharmacologically stimulate deep breathing in the postoperative patient. (A quantitative method of assessing oxygenation, such as pulse oximetry, is recommended.)

### **Drug-Induced Central Nervous System Depression**

Exercising care to prevent vomiting and aspiration, doxapram may be used to stimulate respiration, hasten arousal, and to encourage the return of laryngopharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdosage.

### **Chronic Pulmonary Disease Associated with Acute Hypercapnia**

Doxapram is indicated as a temporary measure in hospitalized patients with acute respiratory insufficiency superimposed on chronic obstructive pulmonary disease. Its use should be for a short period of time (see **DOSAGE AND ADMINISTRATION**) as an aid in the prevention of elevation of arterial CO<sub>2</sub> tension during the administration of oxygen.

It should not be used in conjunction with mechanical ventilation.

## **CONTRAINDICATIONS**

Doxapram is contraindicated in patients with known hypersensitivity to the drug or any of the injection components.

Doxapram should not be used in patients with epilepsy or other convulsive disorders.

Doxapram is contraindicated in patients with proven or suspected pulmonary embolism.

Doxapram is contraindicated in patients with mechanical disorders of ventilation such as mechanical obstruction, muscle paresis (including neuromuscular blockade), flail chest, pneumothorax, acute bronchial asthma, pulmonary fibrosis, or other conditions resulting in restriction of the chest wall, muscles of respiration, or alveolar expansion.

Doxapram is contraindicated in patients with evidence of head injury, cerebral vascular accident, or cerebral edema, and in those with significant cardiovascular impairment, uncompensated heart failure, severe coronary artery disease, or severe hypertension, including that associated with hyperthyroidism or pheochromocytoma. (See **WARNINGS**.)

## **WARNINGS**

Doxapram should not be used in conjunction with mechanical ventilation.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **PRECAUTIONS, Pediatric Use**).

### **In Postanesthetic Use**

- a. Doxapram is neither an antagonist to muscle relaxant drugs nor a specific narcotic antagonist. More specific tests (eg, peripheral nerve stimulation, airway pressures, head lift, pulse oximetry, and end-tidal carbon dioxide) to assess adequacy of ventilation are recommended before administering doxapram.
- b. Doxapram should be administered with great care and only under careful supervision to patients with hypermetabolic states such as hyperthyroidism or pheochromocytoma.
- c. Since narcosis may recur after stimulation with doxapram, care should be taken to maintain close observation until the patient has been fully alert for ½ to 1 hour.
- d. In patients who have received general anesthesia utilizing a volatile agent known to sensitize the myocardium to catecholamines, administration of doxapram should be delayed until the volatile agent has been excreted in order to lessen the potential for arrhythmias, including ventricular tachycardia and ventricular fibrillation (see **PRECAUTIONS, Drug Interactions**).

### **In Drug-Induced CNS and Respiratory Depression**

Doxapram alone may not stimulate adequate spontaneous breathing or provide sufficient arousal in patients who are *severely* depressed either due to respiratory failure or to CNS depressant drugs, but may be used as an adjunct to established supportive measures and resuscitative techniques.

### **In Chronic Obstructive Pulmonary Disease**

Because of the associated increased work of breathing, do not increase the rate of infusion of doxapram in severely ill patients in an attempt to lower pCO<sub>2</sub>.

## **PRECAUTIONS**

### **General**

- a. An adequate airway is essential and airway protection should be considered since doxapram may stimulate vomiting.

- b. Recommended dosages of doxapram should be employed and maximum total dosages should not be exceeded. In order to avoid side effects, it is advisable to use the minimum effective dosage.
- c. Monitoring of the blood pressure, pulse rate, and deep tendon reflexes is recommended to prevent overdosage.
- d. Vascular extravasation or use of a single injection site over an extended period should be avoided since either may lead to thrombophlebitis or local skin irritation.
- e. Rapid infusion may result in hemolysis.
- f. Lowered  $p\text{CO}_2$  induced by hyperventilation produces cerebral vasoconstriction and slowing of the cerebral circulation. This should be taken into consideration on an individual basis. In certain patients a pressor effect of doxapram on the pulmonary circulation may result in a fall of the arterial  $p\text{O}_2$  probably due to a worsening of ventilation perfusion-matching in the lungs despite an overall improvement in alveolar ventilation and a fall in  $p\text{CO}_2$ . Patients should be carefully supervised taking into account available blood gas measurements.
- g. There is a risk that doxapram will produce adverse effects (including seizures) due to general central nervous system stimulation. Muscle involvement may range from fasciculation to spasticity. Anticonvulsants such as intravenous short-acting barbiturates, along with oxygen and resuscitative equipment should be readily available to manage overdosage manifested by excessive central nervous system stimulation. Slow administration of the drug and careful observation of the patient during administration and for some time subsequently are advisable. These precautions are to assure that the protective reflexes have been restored and to prevent possible post-hyperventilation or hypoventilation.
- h. Doxapram should be administered cautiously to patients receiving sympathomimetic or monoamine oxidase inhibiting drugs, since an additive pressor effect may occur.
- i. Blood pressure increases are generally modest but significant increases have been noted in some patients. Because of this, doxapram is not recommended for use in patients with severe hypertension (see **CONTRAINDICATIONS**).
- j. Cardiovascular effects may include various dysrhythmias. Patients receiving doxapram should be monitored for disturbance of their cardiac rhythm.
- k. If sudden hypotension or dyspnea develops, doxapram should be stopped.
- l. Doxapram should be administered with caution to patients with significantly impaired hepatic or renal function as a reduction in the rate of metabolism or excretion of metabolites may alter the response.

### **In Postanesthetic Use**

- a. The same consideration to pre-existing disease states should be exercised as in non-anesthetized individuals. See **CONTRAINDICATIONS** and **WARNINGS** covering use in hypertension, asthma, disturbances of respiratory mechanics including airway obstruction, CNS disorders including increased cerebrospinal fluid pressure, convulsive disorders, acute agitation, and profound metabolic disorders.

- b. See **PRECAUTIONS, Drug Interactions**.

#### **In Chronic Obstructive Pulmonary Disease**

- a. Arrhythmias seen in some patients in acute respiratory failure secondary to chronic obstructive pulmonary disease are probably the result of hypoxia. Doxapram should be used with caution in these patients.
- b. Arterial blood gases should be drawn prior to the initiation of doxapram infusion and oxygen administration, then at least every ½ hour during the infusion period to prevent development of CO<sub>2</sub> retention and acidosis in patients with chronic obstructive pulmonary disease with acute hypercapnia. Doxapram administration does not diminish the need for careful monitoring of the patient or the need for supplemental oxygen in patients with acute respiratory failure. Doxapram should be stopped if the arterial blood gases deteriorate, and mechanical ventilation should be initiated.

#### **Drug Interactions**

Administration of doxapram to patients who are receiving sympathomimetic or monoamine oxidase inhibiting drugs may result in an additive pressor effect (see **PRECAUTIONS, General**).

In patients who have received neuromuscular blocking agents, doxapram may temporarily mask the residual effects of these drugs.

In patients who have received general anesthesia utilizing a volatile agent known to sensitize the myocardium to catecholamines, administration of doxapram should be delayed until the volatile agent has been excreted in order to lessen the potential for arrhythmias, including ventricular tachycardia and ventricular fibrillation (see **WARNINGS**).

There may be an interaction between doxapram and aminophylline and between theophylline manifested by increased skeletal muscle activity, agitation, and hyperactivity.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No carcinogenic or mutagenic studies have been performed using doxapram. Doxapram did not adversely affect the breeding performance of rats.

#### **Pregnancy**

##### **Pregnancy Category B**

Reproduction studies have been performed in rats at doses up to 1.6 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to doxapram. There are, however, no adequate and well-controlled studies in pregnant women. Because the animals in the reproduction studies were dosed by the IM and oral routes and animal reproduction studies, in general, are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

#### **Nursing Mothers**

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 doxapram hydrochloride is administered to a nursing woman.

## **Pediatric Use**

Safety and effectiveness in pediatric patients below the age of 12 years have not been established. This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Premature neonates given doxapram have developed hypertension, irritability, jitteriness, hyperglycemia, glucosuria, abdominal distension, increased gastric residuals, vomiting, bloody stools, necrotizing enterocolitis, erratic limb movements, excessive crying, disturbed sleep, premature eruption of teeth, and QT prolongation that has resulted in heart block. In premature neonates with risk factors such as a previous seizure, perinatal asphyxia, or intracerebral hemorrhage, seizures have occurred. In many instances, doxapram was administered following administration of xanthine derivatives such as caffeine, aminophylline or theophylline.

## **ADVERSE REACTIONS**

Adverse reactions reported coincident with the administration of DOPRAM (doxapram hydrochloride, USP) include:

### **1. Central and Autonomic Nervous Systems**

Pyrexia, flushing, sweating; pruritus and paresthesia, such as a feeling of warmth, burning, or hot sensation, especially in the area of genitalia and perineum; apprehension, disorientation, pupillary dilatation, hallucinations, headache, dizziness, hyperactivity, involuntary movements, muscle spasticity, muscle fasciculations, increased deep tendon reflexes, clonus, bilateral Babinski, and convulsions.

### **2. Respiratory**

Dyspnea, cough, hyperventilation, tachypnea, laryngospasm, bronchospasm, hiccough, and rebound hypoventilation.

### **3. Cardiovascular**

Phlebitis, variations in heart rate, lowered T-waves, arrhythmias (including ventricular tachycardia and ventricular fibrillation), chest pain, tightness in chest. A mild to moderate increase in blood pressure is commonly noted and may be of concern in patients with severe cardiovascular diseases.

#### **4. Gastrointestinal**

Nausea, vomiting, diarrhea, desire to defecate.

#### **5. Genitourinary**

Stimulation of urinary bladder with spontaneous voiding; urinary retention. Elevation of BUN and albuminuria.

#### **6. Hemic and Lymphatic**

Hemolysis with rapid infusion. A decrease in hemoglobin, hematocrit, or red blood cell count has been observed in postoperative patients. In the presence of pre-existing leukopenia, a further decrease in WBC has been observed following anesthesia and treatment with doxapram hydrochloride.

### **OVERDOSAGE**

#### **Signs and Symptoms**

Symptoms of overdosage are extensions of the pharmacologic effects of the drug. Excessive pressor effect, such as hypertension, tachycardia, skeletal muscle hyperactivity, and enhanced deep tendon reflexes may be early signs of overdosage. Therefore, the blood pressure, pulse rate, and deep tendon reflexes should be evaluated periodically and the dosage or infusion rate adjusted accordingly.

Other effects may include agitation, confusion, sweating, cough, and dyspnea.

Convulsive seizures are unlikely at recommended dosages. In unanesthetized animals, the convulsant dose is 70 times greater than the respiratory stimulant dose. Intravenous LD<sub>50</sub> values in the mouse and rat were approximately 75 mg/kg and in the cat and dog were 40 to 80 mg/kg.

Except for management of chronic obstructive pulmonary disease associated with acute hypercapnia, the maximum recommended dosage is 3 GRAMS/24 HOURS. (See

#### **DOSAGE AND ADMINISTRATION.)**

#### **Management**

There is no specific antidote for doxapram. Management should be symptomatic. Anticonvulsants, along with oxygen and resuscitative equipment should be readily available to manage overdosage manifested by excessive central nervous system stimulation. Slow administration of the drug and careful observation of the patient during administration and for some time subsequently are advisable. These precautions are to assure that the protective reflexes have been restored and to prevent possible post-hyperventilation or hypoventilation.

There is no evidence that doxapram is dialyzable; further, the half-life of doxapram makes it unlikely that dialysis would be appropriate in managing overdose with this drug.

### **DOSAGE AND ADMINISTRATION**

**NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS)**

## In Postanesthetic Use

**Table I. Dosage for postanesthetic use—I.V. and infusion.**

I.V. Administration	Recommended Dosage mg/kg	Maximum dose per single injection mg/kg	Maximum total dose* mg/kg
Single Injection	0.5-1	1.5	1.5
Repeat Injections (5 min. intervals)	0.5-1	1.5	2
Infusion	0.5-1	—	4

**\*Dose not to exceed 3 grams/24 hours.**

### By I.V. Injection

(See Table I. Dosage for postanesthetic use—I.V.)

The recommended dose for I.V. administration is 0.5 – 1 mg/kg for a single injection and at 5-minute intervals. Careful observation of the patient during administration and for some time subsequently are advisable. The maximum total dosage by I.V. injection is 2 mg/kg.

### By Infusion

The solution is prepared by adding 250 mg of doxapram (12.5 mL) to 250 mL of dextrose 5% or 10% in water or normal saline solution. The infusion is initiated at a rate of approximately 5 mg/minute until a satisfactory respiratory response is observed, and maintained at a rate of 1 to 3 mg/minute. The rate of infusion should be adjusted to sustain the desired level of respiratory stimulation with a minimum of side effects. The maximum total dosage by infusion is 4 mg/kg, or approximately 300 mg for the average adult.

## In the Management of Drug-Induced CNS Depression

(See Table II. Dosage for drug-induced CNS depression.)

**Table II. Dosage for drug-induced CNS depression.**

Level of Depression	METHOD ONE	METHOD TWO
	Priming dose single/repeat I.V. Injection mg/kg	Rate of Intermittent I.V. Infusion mg/kg/hr
Mild*	1	1-2
Moderate†	2	2-3

### \*Mild Depression

Class 0: Asleep, but can be aroused and can answer questions.

Class 1: Comatose, will withdraw from painful stimuli, reflexes intact.

### †Moderate Depression

Class 2: Comatose, will not withdraw from painful stimuli, reflexes intact.

Class 3: Comatose, reflexes absent, no depression of circulation or respiration.

## Method One

### Using Single and/or Repeat Single I.V. Injections

- Give priming dose of 2 mg/kg body weight and repeat in 5 minutes. The priming dose for moderate depression is 2 mg/kg and the priming dose for mild depression is 1 mg/kg.

- b. Repeat same dose q 1 to 2h until patient awakens. Watch for relapse into unconsciousness or development of respiratory depression, since DOPRAM does not affect the metabolism of CNS-depressant drugs.
- c. If relapse occurs, resume injections q 1 to 2h until arousal is sustained, or total maximum daily dose (3 grams) is given. After maximum dose has been given (3 grams), allow patient to sleep until 24 hours have elapsed from first injection of DOPRAM, using assisted or automatic respiration if necessary.
- d. Repeat procedure the following day until patient breathes spontaneously and sustains desired level of consciousness, or until maximum dosage (3 grams) is given.
- e. Repetitive doses should be administered only to patients who have shown response to the initial dose.
- f. Failure to respond appropriately indicates the need for neurologic evaluation for a possible central nervous system source of sustained coma.

### **Method Two**

#### **By Intermittent I.V. Infusion**

- a. Give priming dose as in Method One.
- b. If patient awakens, watch for relapse; if no response, continue general supportive treatment for 1 to 2 hours and repeat priming dose of DOPRAM. If some respiratory stimulation occurs, prepare I.V. infusion by adding 250 mg of DOPRAM (12.5 mL) to 250 mL of saline or dextrose solution. Deliver at rate of 1 to 3 mg/min (60 to 180 mL/hr) according to size of patient and depth of coma. Discontinue DOPRAM if patient begins to waken or at end of 2 hours.
- c. Continue supportive treatment for ½ to 2 hours and repeat Step b.
- d. Do not exceed 3 grams/day.

### **Chronic Obstructive Pulmonary Disease Associated with Acute Hypercapnia**

- a. One vial of doxapram (400 mg) should be mixed with 180 mL of dextrose 5% or 10% or normal saline solution (concentration of 2 mg/mL). The infusion should be started at 1 to 2 mg/minute (½ to 1 mL/minute); if indicated, increase to a maximum of 3 mg/minute. Arterial blood gases should be determined prior to the onset of doxapram's administration and at least every half hour during the two hours of infusion to insure against the insidious development of CO<sub>2</sub>-RETENTION AND ACIDOSIS. Alteration of oxygen concentration or flow rate may necessitate adjustment in the rate of doxapram infusion.
- b. Predictable blood gas patterns are more readily established with a continuous infusion of doxapram. If the blood gases show evidence of deterioration, the infusion of doxapram should be discontinued.
- c. ADDITIONAL INFUSIONS BEYOND THE SINGLE MAXIMUM TWO HOUR ADMINISTRATION PERIOD ARE NOT RECOMMENDED.

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

**Diluent Compatibility**

Doxapram hydrochloride is compatible with 5% and 10% dextrose in water or normal saline.

**Incompatibility**

ADMIXTURE OF DOXAPRAM WITH ALKALINE SOLUTIONS SUCH AS 2.5% THIOPENTAL SODIUM, SODIUM BICARBONATE, FUROSEMIDE, OR AMINOPHYLLINE WILL RESULT IN PRECIPITATION OR GAS FORMATION.

Doxapram is also not compatible with ascorbic acid, cefoperazone sodium, cefotaxime sodium, cefotetan sodium, cefuroxime sodium, folic acid, dexamethasone disodium phosphate, diazepam, hydrocortisone sodium phosphate, methylprednisolone sodium, or hydrocortisone sodium succinate.

Admixture of doxapram and ticarcillin disodium results in an 18% loss of doxapram in 3 hours. When doxapram is mixed with minocycline hydrochloride, there is a loss of 8% of doxapram in 3 hours and a 13% loss of doxapram in 6 hours.

**HOW SUPPLIED**

DOPRAM Injection (doxapram hydrochloride injection, USP) containing 20 mg of doxapram hydrochloride per mL with benzyl alcohol 0.9% as the preservative is available in:

20 mL multiple dose vials in packages of 6 (NDC 60977-144-02).

**CONTAINS BENZYL ALCOHOL.**

**Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].**

ESI Stylized Logo and Dopram are trademarks of Baxter International Inc., or its subsidiaries.



Manufactured by  
**Baxter Healthcare Corporation**  
Deerfield, IL 60015 USA

For Product Inquiry 1 800 ANA DRUG (1-800-262-3784)

MLT-31/2.0

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**14-879 / S-044**

**ADMINISTRATIVE DOCUMENTS**  
**AND**  
**CORRESPONDENCE**

## Division of Anesthetic, Critical Care, and Addiction Drug Products

### REGULATORY PROJECT MANAGER REVIEW

<b>Application Number:</b>	NDA 14-879/S-044	NDA 14-879/S-044
<b>Name of Drug:</b>	Dopram hydrochloride Injection, USP	Dopram hydrochloride Injection, USP
<b>Sponsor:</b>	Baxter	Baxter
<b>Submission Date(s):</b>	September 16, 2004	December 22, 2004
<b>Receipt Date(s):</b>	September 17, 2004	December 23, 2004

#### Material Reviewed:

NDA 14-879/S-044

#### Background and Summary Description:

The supplement (S-043) dated January 19, 2004 provide change in the rubber formulation for                      he new stopper does not contain dry natural rubber (latex) therefore the labeling was revised to reflect this change.

This supplement application (S-044) dated September 16, 2004 and amendment (S-044) dated December 22, 2004, provide for removal of statements containing "dry natural rubber" through out the labeling (contains revised package insert, carton and container labels).

The text of the revised labels was compared to the text of last approved label (NDA 14-879/040; Submission date October 14, 2003) and Approval letter dated April 16, 2004.

#### Status Report

**Reviews Completed:** Pratibha Rana, M.S, RPM, February 14, 2005

**Reviews Pending:** Medical Officer

#### RPM Review

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label.

## **PACKAGE INSERT**

**TITLE:** No change noted.

**BOX WARNING:** NA

**DESCRIPTION:**

~~The vial stopper in this product contains dry natural rubber (latex).~~

**CLINICAL PHARMACOLOGY:** No change noted

**INDICATIONS AND USAGE:** No change noted

**CONTRAINDICATIONS:** No change noted

**WARNINGS:**

~~The vial stopper in this product contains dry natural rubber that may cause hypersensitivity reactions when handled by or when the product is injected in persons with known possible latex sensitivity.~~

**PRECAUTIONS:** No change noted.

**ADVERSE REACTIONS:** No change noted.

**DRUG ABUSE AND DEPENDENCE:** No change noted.

**OVERDOSAGE:** No change noted

**DOSAGE AND ADMINISTRATION:** No change was noted.

**HOW SUPPLIED:**

~~The vial stopper in this product contains dry natural rubber that may cause hypersensitivity reactions when handled by or when the product is injected in persons with known or possible latex sensitivity.~~

## **IMMEDIATE CONTAINER LABEL**

400mg/20 ml was added in front of 20mg/ml

The following was move to the right side of the label:

Water for Injection, USP q.s./Benzyl Alcohol, NF (preservative) 0.9%

The Baxter logo was changed to ESI.

## **INDIVIDUAL CARTON LABEL**

### **Carton Top:**

The total strength per vial 400mg/20ml was added.

### **Back panel:**

No change noted.

Left and Right Side Panel:

400mg/20ml

~~Benzyl Alcohol, NF (preservative) 0.9%~~

~~Water for Injection, USP..... q.s.~~ was relocated to the side panel to read:

Water for Injection, USP q.s./Benzyl Alcohol, NF (preservative) 0.9%

## **SIX PACK CARTON LABEL**

The total strength per vial 400mg/20ml was added to top and side panels.

~~Benzyl Alcohol, NF (preservative) 0.9%~~

~~Water for Injection, USP..... q.s.~~

Was removed from top, front, and right panels and added to the side panel:

Water for Injection, USP q.s./Benzyl Alcohol, NF (preservative) 0.9%

## **RECOMMENDATIONS**

Pratibha Rana, Regulatory Project Manager/ Approval/February 14, 2005

Dr. Art Simone, Medical Officer, concurred with this review on March 9, 2005

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

/s/

-----  
Pratibha Rana  
3/10/05 10:05:58 AM  
CSO

Parinda Jani  
3/11/05 01:07:29 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 14-879/S-044

**CBE-30/CBE-0 SUPPLEMENT**

Baxter Healthcare Corporation  
Anesthesia & Critical Care  
95 Spring Street  
New Providence, NJ 07974

Attention: Laura Cooper  
Manager, Drug Regulatory Affairs

Dear Ms. Cooper:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Dopram® Injectable (doxapram hydrochloride injection, USP)  
NDA Number: 14-879  
Supplement number: 044  
Date of supplement: September 16, 2004  
Date of receipt: September 17, 2004

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes changes to the label to reflect that the new stopper does not contain dry natural rubber (latex).

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on November 16, 2004 in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be March 16, 2005.

All communications concerning this supplement should be addressed as follows:

FDA  
Center for Drug Evaluation and Research  
Division of Anesthetics, Critical Care, and Addiction Drug Products, HFD-170  
Attention: Document Room 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any question, call me, at (301) 827-7431.

Sincerely,

*{See appended electronic signature page}*

Allison Meyer  
Regulatory Project Manager  
Division of Anesthetics, Critical Care  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research