CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-615/S-012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-615/S-012

APR 17 2001

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Route 120 and Wilson Road
Round Lake, IL 60073-0490

Dear Ms. Marconi:

Please refer to your supplemental new drug application dated June 22, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dopamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container, PL 2207.

We acknowledge receipt of your submission dated March 27, 2001 that constituted a complete response to our April 20, 2000 approvable letter.

This supplemental new drug application provides for final printed labeling revised as follows:

1. The **PRECAUTIONS, Pediatric Use** subsection has been changed to:

   Safety and effectiveness in children have not been established. The clearance of dopamine is affected by age (as much as 2 fold greater in children under 2 years of age), renal and hepatic function (decreasing by 2 fold in the presence of either). In younger children, particularly neonates, clearance is highly variable. Newborn infants may be more sensitive to the vasoconstrictive effects of dopamine.

   The most consistent effects of dopamine in 57 publications (between the years 1966 through 1997) were increases in systolic and mean arterial pressure. Renal function was variably affected, except that in a single publication renal function was preserved in the face of treatment with indomethacin. No consistent effect on heart rate was described. Because of the variability of clearance, especially in the neonate and newborn, low doses of dobutamine and slow deliberate titration should be employed (see **DOSAGE and ADMINISTRATION).**

2. Under **DOSAGE and ADMINSTRATION**, a new **Pediatric Dosing and Administration** subsection has been added. It reads as follows:

   Pediatric Dosing and Administration

   In publications, the most common **starting** doses were **1-5** micrograms/kilograms/minute. **Particularly in neonates, such low doses require considerable dilution of this product; careful consideration should be given to the use of this product in such circumstances.** Dosing increments that were reported ranged from 2.5 to 5.0 micrograms/kilogram/minute. Usual maximum doses were 15-20 micrograms/kilogram/minute, with occasional use as great as 50 micrograms/kilogram/minute. The time course of dopamine kinetics are poorly defined. Increasing infusion rates (or dose) should be approached cautiously and only after it is apparent that hemodynamics (mainly systolic blood pressure) have stabilized with respect to the current dose and/or rate of infusion.

There have been occasional reports of vasospastic events when dopamine was infused through umbilical vessels. Due caution should be exercised if infusion of dopamine through umbilical vessels becomes necessary.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your submission of March 27, 2001). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely, /S/

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-615/S-012

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

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NDA 19-615/S-012

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Route 120 and Wilson Road
Round Lake, IL 60073-0490

Dear Ms. Marconi:

Please refer to your new drug application (NDA) dated June 22, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dopamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container, PL 2207.

The supplemental application provides for draft labeling revised as required in the December 13, 1994 Federal Register notice relating to the revision of the "Pediatric Use" subsection . It also provides for revisions of the **WARNINGS** and **PRECAUTIONS** sections of the labeling to include information regarding pediatric patients.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. Please retain, under **WARNINGS**, the second paragraph, which read "Evidence is inadequate for fully defining proper dosage and limitations for use in children."

2. Please delete your proposed additions to the **WARNINGS** section (Inserts A and B).

3. The **PRECAUTIONS, Pediatric Use** subsection should be revised to read as follows:

   Safety and effectiveness in children have not been established. The clearance of dopamine is affected by age (as much as 2 fold greater in children under 2 years of age), renal and hepatic function (decreasing by 2 fold in the presence of either). In younger children, particularly neonates, clearance is highly variable. Newborn infants may be more sensitive to the vasoconstrictive effects of dopamine.

   The most consistent effects of dopamine in 57 publications (between the years 1966 through 1997) were increases in systolic and mean arterial pressure. Renal function was variably affected, except that in a single publication renal function was preserved in the face of treatment with indomethacin. No consistent effect on heart rate was described. Because of the variability of clearance, especially in the neonate and newborn, low doses of dobutamine and slow deliberate titration should be employed (see **DOSAGE and ADMINISTRATION**).

4. Please delete your proposed addition to the **DOSAGE and ADMINISTRATION** section (Insert C).

5. Under **DOSAGE and ADMINISTRATION**, a new **Pediatric Dosing and Administration** subsection has been established. This subsection should be inserted after the sentence that reads "Drug additives should not be made to Dopamine Hydrochloride and 5% Dextrose Injection, USP." and should read as follows:

   Pediatric Dosing and Administration

   In publications, the most common **starting** doses were **1-5** micrograms/kilograms/minute. **Particularly in neonates, such low doses require considerable dilution of this product; careful consideration should be given to the use of this product in such circumstances.** Dosing increments that were reported ranged from 2.5 to 5.0 micrograms/kilogram/minute. Usual maximum doses were 15-20 micrograms/kilogram/minute, with occasional use as great as 50 micrograms/kilogram/minute. The time course of dopamine kinetics are poorly defined. Increasing infusion rates (or dose) should be approached cautiously and only after it is apparent that hemodynamics (mainly systolic blood pressure) have stabilized with respect to the current dose and/or rate of infusion.

   There have been occasional reports of vasospastic events when dopamine was infused through umbilical vessels. Due caution should be exercised if infusion of dopamine through umbilical vessels becomes necessary.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Project Manager
(301) 594-5313

Sincerely,

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-615/S-012

FINAL PRINTED LABELING

Baxter

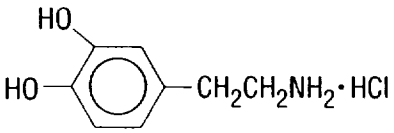
Dopamine Hydrochloride and 5% Dextrose Injection, USP

in Plastic Container

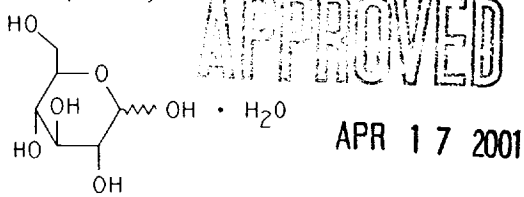
Viaflex® Plus Container

Description

Dopamine Hydrochloride and 5% Dextrose Injection, USP is a sterile, nonpyrogenic solution of Dopamine Hydrochloride, USP and Dextrose, USP in Water for Injection. Structural formulas are shown below:



Dopamine Hydrochloride, USP



Dextrose Hydrous, USP
(D-Glucopyranose monohydrate)

Dopamine Hydrochloride and 5% Dextrose Injection, USP is intended for intravenous use only. It contains no antimicrobial agents. The pH is adjusted with hydrochloric acid and is 3.5 (2.5 to 4.5). Approximately 5 mEq/L sodium bisulfite is added as a stabilizer. The solution provides a caloric content of 170 kcal/L. The solution is intended for single use only. When smaller doses are required, the unused portion should be discarded. Composition and osmolarity are given below:

800 mcg/mL Dopamine Hydrochloride and 5% Dextrose Injection, USP provides 800 mcg/mL Dopamine Hydrochloride, USP and 50 g/L Dextrose Hydrous, USP with an osmolarity of 261 mOsmol/L (calc).

1600 mcg/mL Dopamine Hydrochloride and 5% Dextrose Injection, USP provides 1600 mcg/mL Dopamine Hydrochloride, USP and 50 g/L Dextrose Hydrous, USP with an osmolarity of 269 mOsmol/L (calc).

3200 mcg/mL Dopamine Hydrochloride and 5% Dextrose Injection, USP provides 3200 mcg/mL Dopamine Hydrochloride, USP and 50 g/L Dextrose Hydrous, USP with an osmolarity of 286 mOsmol/L (calc).

Dopamine administered intravenously is a myocardial inotropic agent which also may increase mesenteric and renal blood flow plus urinary output.

Dopamine hydrochloride is designated chemically as 3,4-dihydroxyphenethylamine hydrochloride, a white crystalline powder freely soluble in water. Dopamine (also referred to as 3-hydroxytyramine) is a naturally occurring biochemical catecholamine precursor of norepinephrine.

This Viaflex® Plus plastic container is fabricated from a specially formulated polyvinyl chloride (PL 2207 Plastic). Viaflex® containers, including Viaflex® Plus containers, are made of flexible plastic and are for parenteral use. Viaflex® Plus on the container indicates the presence of a drug additive in a drug vehicle. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

Clinical Pharmacology

Dopamine is a natural catecholamine formed by the decarboxylation of 3,4-dihydroxyphenylalanine (DOPA). It is a precursor to norepinephrine in noradrenergic nerves and is also a neurotransmitter in certain areas of the central nervous system, especially in the nigrostriatal tract, and in a few peripheral sympathetic nerves.

Dopamine produces positive chronotropic and inotropic effects on the myocardium, resulting in increased heart rate and cardiac contractility. This is accomplished directly by exerting an agonist action on beta-adrenoceptors and indirectly by causing release of norepinephrine from storage sites in sympathetic nerve endings.

Dopamine's onset of action occurs within five minutes of intravenous administration, and with dopamine's plasma half-life of about two minutes, the duration of action is less than ten minutes. If monoamine oxidase (MAO) inhibitors are present, however, the duration may increase to one hour. The drug is widely distributed in the body but does not cross the blood-brain barrier to a significant extent. Dopamine is metabolized in the liver, kidney, and plasma by MAO and catechol-O-methyltransferase to the inactive compounds homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid. About 25% of the dose is taken up into specialized neurosecretory vesicles (the adrenergic nerve terminals), where it is hydroxylated to form norepinephrine. It has been reported that about 80% of the drug is excreted in the urine within 24 hours, primarily as HVA and its sulfate and glucuronide conjugates and as 3,4-dihydroxyphenylacetic acid. A very small portion is excreted unchanged.

The predominant effects of dopamine are dose-related, although actual response of an individual patient will largely depend on the clinical status of the patient at the time the drug is administered. At low rates of infusion (0.5-2 mcg/kg/min) dopamine causes vasodilation that is presumed to be due to a specific agonist action on dopamine receptors (distinct from alpha- and beta-adrenoceptors) in the renal, mesenteric, coronary, and intracerebral vascular beds. At these dopamine receptors, haloperidol is an antagonist. The vasodilation in these vascular beds is accompanied by increased glomerular filtration rate, renal blood flow, sodium excretion, and urine flow. Hypotension sometimes occurs. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolarity of the urine.

At intermediate rates of infusion (2-10 mcg/kg/min) dopamine acts to stimulate the $beta_1$-adrenoceptors, resulting in improved myocardial contractility, increased SA rate and enhanced impluse conduction in the heart. There is little, if any, stimulation of the $beta_2$-adrenoceptors (peripheral vasodilation). Dopamine causes less increase in myocardial oxygen consumption than isoproterenol, and its use is not usually associated with a tachyarrhythmia. Clinical studies indicate that it usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Blood flow to the peripheral vascular beds may decrease while mesenteric flow increased due to increased cardiac output. At low and intermediate doses, total peripheral resistance (which would be raised by alpha activity) is usually unchanged.

At higher rates of infusion (10-20 mcg/kg/min) there is some effect on alpha-adrenoceptors, with consequent vasoconstrictor effects and a rise in blood pressure. The vasoconstrictor effects are first seen in the skeletal muscle vascular beds, but with increasing doses they are also evident in the renal and mesenteric vessels. At very high rates of infusion (above 20 mcg/kg/min), stimulation of alpha-adrenoceptors predominates and vasoconstriction may compromise the circulation of the limbs and override the dopaminergic effects of dopamine, reversing renal dilation and natriuresis.

Dextrose provides a source of calories. Dextrose is readily metabolized, may decrease losses of body protein and nitrogen, promotes glycogen deposition and decreases or prevents ketosis if sufficient doses are provided.

Indications and Usage

Dopamine hydrochloride is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of dopamine hydrochloride.

Patients most likely to respond adequately to dopamine hydrochloride are those in whom physiological parameters, such as urine flow, myocardial function and blood pressure have not undergone profound deterioration. Reports indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and dopamine hydrochloride, the better the prognosis.

Poor Perfusion of Vital Organs - Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Reported studies indicate that when dopamine hydrochloride is administered before urine flow has diminished to levels of approximately 0.3 mL/minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of dopamine hydrochloride has resulted in an increase in urine flow which in some cases reached normal levels. Dopamine hydrochloride may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of preexisting fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of dopamine hydrochloride and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output - Increased cardiac output is related to dopamine hydrochloride's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g., femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by dopamine hydrochloride is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension - Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of dopamine hydrochloride, which have little effect on SVR. At high therapeutic doses, dopamine hydrochloride's alpha-adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer dopamine hydrochloride as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

Contraindications

Dopamine hydrochloride should not be used in patients with pheochromocytoma.

Dopamine hydrochloride should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

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

Warnings

Patients who have been treated with monoamine oxidase (MAO) inhibitors prior to the administration of dopamine hydrochloride will require substantially reduced dosage. See Drug Interactions, below.

Evidence is inadequate for fully defining proper dosage and limitations for use in children.

Contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Do **not** add Dopamine Hydrochloride and 5% Dextrose Injection, USP to any alkaline diluent solution since dopamine hydrochloride is inactivated in alkaline solution.

Solutions containing dextrose 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, congested states or pulmonary edema.

Excess administration of potassium-free solutions may result in significant hypokalemia.

Precautions

General

Avoid bolus administration of dopamine hydrochloride. See **Dosage and Administration**.

Avoid Hypovolemia - Prior to treatment with dopamine hydrochloride, hypovolemia should be fully corrected, if possible, with either whole blood, plasma, or plasma expanders as indicated. Monitoring of central venous pressure or left ventricular filling pressure may be helpful in detecting and treating hypovolemia.

Hypoxia, Hypercapnia, Acidosis - These conditions, which may also reduce the effectiveness and/or increase the incidence of adverse effects of dopamine, must be identified and corrected prior to, and concurrently with, administration of dopamine HCl.

Ventricular Arrhythmias - If an increased number of ectopic beats is observed, the dose should be reduced if possible.

Decreased Pulse Pressure - If a disproportionate rise in the diastolic pressure (i.e., marked decrease in the pulse pressure) is observed in patients receiving dopamine hydrochloride, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Hypotension - At lower infusion rates, if hypotension occurs, the infusion rate should be rapidly increased until adequate blood pressure is obtained. If hypotension persists, dopamine HCl should be discontinued and a more potent vasoconstrictor agent such as norepinephrine should be administered.

Occlusive Vascular Disease - Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued dopamine hydrochloride infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing the rate or discontinuing the infusion.

Extravasation - Dopamine Hydrochloride and 5% Dextrose Injection, USP should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

IMPORTANT - Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 mL of 0.9% Sodium Chloride Injection, USP containing from 5 to 10 mg phentolamine, an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockage with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Weaning - When discontinuing the infusion, it may be necessary to gradually decrease the dose of dopamine HCl while expanding blood volume with IV fluids, since sudden cessation may result in marked hypotension.

Careful Monitoring Required - Close monitoring of the following indices - urine flow, cardiac output and blood pressure - during dopamine hydrochloride infusion is necessary as in the case of any adrenergic agent.

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

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

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.

Laboratory Tests

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations and acid base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

Drug Interactions

Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and may sensitize the myocardium to the action of certain intravenously administered catecholamines, such as dopamine. This interaction appears to be related both to pressor activity and to the beta-adrenergic stimulating properties of these catecholamines, and may produce ventricular arrhythmias. Therefore, EXTREME CAUTION should be exercised when administering dopamine HCl to patients receiving cyclopropane or halogenated hydrocarbon anesthetics. Results of studies in animals indicate that dopamine-induced ventricular arrhythmias during anesthesia can be reversed by propranolol.

Because dopamine is metabolized by monoamine oxidase (MAO), inhibition of this enzyme prolongs and potentiates the effect of dopamine. Patients who have been treated with MAO inhibitors within two to three weeks prior to the administration of dopamine should receive initial doses of dopamine hydrochloride no greater than one-tenth (1/10) of the usual dose.

Concurrent administration of low-dose dopamine HCl and diuretic agents may produce an additive or potentiating effect on urine flow.

Tricyclic antidepressants may potentiate the cardiovascular effects of adrenergic agents.

Cardiac effects of dopamine are antagonized by beta-adrenergic blocking agents, such as propranolol and metoprolol. The peripheral vasoconstriction caused by high doses of dopamine HCl is antagonized by alpha-adrenergic blocking agents. Dopamine-induced renal and mesenteric vasodilation is not antagonized by either alpha- or beta-adrenergic blocking agents.

Butyrophenones (such as haloperidol) and phenothiazines can suppress the dopaminergic renal and mesenteric vasodilation induced with low-dose dopamine infusion.

The concomitant use of vasopressors, vasoconstrictor agents (such as ergonovine) and some oxytocic drugs may result in severe hypertension.

Administration of phenytoin to patients receiving dopamine HCl has been reported to lead to hypotension and bradycardia. It is suggested that in patients receiving dopamine HCl, alternatives to phenytoin should be considered if anticonvulsant therapy is needed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies have not been performed to evaluate the carcinogenic potential of dopamine HCl.

Dopamine HCl at doses approaching maximal solubility showed no clear genotoxic potential in the Ames test. Although there was a reproducible dose-dependent increase in the number of revertant colonies with strains TA100 and TA98, both with and without metabolic activation, the small increase was considered inconclusive evidence of mutagenicity. In the L5178Y TK $\pm$ mouse lymphoma assay, dopamine HCl at the highest concentrations used of 750 µg/ml without metabolic activation, and 3000 µg/ml with activation, was toxic and associated with increases in mutant frequencies when compared to untreated and solvent controls; at the lower concentrations no increases over controls were noted.

No clear evidence of clastogenic potential was reported in the in vivo mouse or male rat bone marrow micronucleus test when the animals were treated intravenously with up to 224 mg/kg and 30 mg/kg of dopamine HCl, respectively.

Pregnancy: Pregnancy Category C.

Teratogenic Effects: Teratogenicity studies in rats and rabbits at dopamine HCl dosages up to 6 mg/kg/day intravenously during organogenesis produced no detectable teratogenic or embryotoxic effects, although maternal toxicity consisting of mortalities, decreased body weight gain, and pharmacotoxic signs were observed in rats. In a published study, dopamine HCl administered at 10 mg/kg subcutaneously for 30 days, markedly prolonged metestrus and increased mean pituitary and ovary weights in female rats. Similar administration to pregnant rats throughout gestation or for 5 days starting on gestation day 10 or 15 resulted in decreased body weight gains, increased mortalities and slight increases in cataract formation among the offspring. There are no adequate and well-controlled studies in pregnant women, and it is not known if dopamine HCl crosses the placental barrier. Dopamine HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

In obstetrics, if vasopressor drugs are used to correct hypotension or are added to a local anesthetic solution the interaction with some oxytocic drugs may cause severe hypertension.

Nursing Mothers

It is not known whether dopamine hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dopamine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established. The clearance of dopamine is affected by age (as much as 2 fold greater in children under 2 years of age), renal and hepatic function (decreasing by 2 fold in the presence of either). In younger children, particularly neonates, clearance is highly variable. Newborn infants may be more sensitive to the vasoconstrictive effects of dopamine.

The most consistent effects of dopamine in 57 publications (between the years 1966 through 1997) were increases in systolic and mean arterial pressure. Renal function was variably affected, except that in a single publication renal function was preserved in the face of treatment with indomethacin. No consistent effect on heart rate was described. Because of the variability of clearance, especially in the neonate and newborn, low doses of dobutamine and slow deliberate titration should be employed (see **DOSAGE and ADMINISTRATION**).

Adverse Reactions

The following adverse reactions have been observed, but there are not enough data to support an estimate of their frequency.

Cardiovascular System

ventricular arrhythmia (at very high doses)
ectopic beats
tachycardia
anginal pain
palpitation
cardiac conduction abnormalities
widened QRS complex
bradycardia
hypotension
hypertension
vasoconstriction

Respiratory System

dyspnea

Gastrointestinal System

nausea
vomiting

Metabolic/Nutritional System

azotemia

Central Nervous System

headache
anxiety

Dermatological System

piloerection

Other

Gangrene of the extremities has occurred when high doses were administered for prolonged periods or in patients with occlusive vascular disease receiving low doses of dopamine HCl.

Overdosage

In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue dopamine hydrochloride until patient's condition stabilizes. Since dopamine hydrochloride's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha-adrenergic blocking agent, phentolamine, should be considered.

Dosage and Administration

Rate of Administration - Dopamine Hydrochloride and 5% Dextrose Injection, USP is administered intravenously through a suitable intravenous catheter or needle. An IV drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with dopamine hydrochloride. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration of dopamine hydrochloride at rates greater than 50 mcg/kg/min has safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, use of a more concentrated solution may be preferred over increasing the flow rate of a less concentrated solution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood, plasma, or plasma expanders until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14 to 18 mm Hg.
2. Begin infusion of Dopamine Hydrochloride and 5% Dextrose Injection, USP at doses of 2 to 5 mcg/kg/min in patients who are likely to respond to modest increments of heart force and renal perfusion.

   In more seriously ill patients, begin administration of Dopamine Hydrochloride and 5% Dextrose Injection, USP at rates of 5 mcg/kg/min and increase gradually using 5 to 10 mcg/kg/min increments up to a rate of 20 to 50 mcg/kg/min as needed. If rates in excess of 50 mcg/kg/min are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of dopamine hydrochloride dosage should be considered. Reports have shown that more than 50% of the patients were satisfactorily maintained on doses of dopamine hydrochloride administered at rates of less than 20 mcg/kg/min. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of dopamine hydrochloride may be given in an effort to produce an appropriate arterial pressure and central perfusion.
3. Treatment of all patients requires constant evaluation of therapy in terms of blood volume, augmentation of myocardial contractility and distribution of peripheral perfusion. Dosage of dopamine hydrochloride should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.
4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

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

Do not use Dopamine Hydrochloride and 5% Dextrose Injection, USP if darker than slightly yellow or discolored in any other way.

All injections in Viaflex® Plus plastic containers are intended for intravenous administration using sterile equipment.

Drug additives should not be made to Dopamine Hydrochloride and 5% Dextrose Injection, USP.

Pediatric Dosing and Administration

In publications, the most common **starting** doses were **1-5** micrograms/kilograms/minute. **Particularly in neonates, such low doses require considerable dilution of this product; careful consideration should be given to the use of this product in such circumstances.** Dosing increments that were reported ranged from 2.5 to 5.0 micrograms/kilogram/minute. Usual maximum doses were 15-20 micrograms/kilogram/minute, with occasional use as great as 50 micrograms/kilogram/minute. The time course of dopamine kinetics are poorly defined. Increasing infusion rates (or dose) should be approached cautiously and only after it is apparent that hemodynamics (mainly systolic blood pressure) have stabilized with respect to the current dose and/or rate of infusion.

There have been occasional reports of vasospastic events when dopamine was infused through umbilical vessels. Due caution should be exercised if infusion of dopamine through umbilical vessels becomes necessary.

How Supplied

Code	Size (mL)	mcg/mL	NDC
2B0832	250	800	0338-1005-02
2B0842	250	1600	0338-1007-02
2B0833	500	800	0338-1005-03
2B0846	250	3200	0338-1009-02
2B0843	500	1600	0338-1007-03

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended the product be stored at room temperature (25ºC); brief exposure up to 40ºC does not adversely affect the product.

Avoid contact with alkalies (including sodium bicarbonate), oxidizing agents or iron salts.

NOTE - Do not use the injection if it is darker than slightly yellow or discolored in any other way.

Directions for use of Viaflex® Plus Plastic Container

The overwrap is a moisture and oxygen barrier. Do not remove unit from overwrap until ready for use.

To open

Tear overwrap down side at notch 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.

Preparation for Administration

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.

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

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Rev. November 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-615-S-012

MEDICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : 4/20/00

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 19-615/S012, Dopamine, Pediatric Labeling, Baxter Health Care

TO : NDA File

In response to the Final Pediatric Use Rule that was published in the Federal Register, Baxter submitted 57 articles that were located by searching Medline and the International Pharmaceutical Abstracts for the years 1966 to 1997, and 1970 to 1997 for Medline and International Pharmaceutical Abstracts, respectively. There were about 710 patients involved in these studies, of which about 516 were exposed to dopamine. The age of patients ranged from preterm to about 16 years of age. There was reasonable representation of neonate and very young children. Routes of administration ranged from intravenous through intra-umbilical artery.

The data in these articles do not represent a coherent development program. Rather, they represent individual investigator initiated small trials that have no relationship to one another. There is not a single trial that evaluated any clinical outcome variable. Consequently, there is no "efficacy" data to evaluate. Similarly, there is no ability to systematically evaluate "safety" form the view of "clinically relevant" endpoints. Anecdotal safety can be evaluated.

In short, although the sponsor hoped to replace "efficacy in pediatric populations has not been established" with "efficacy in pediatric populations has been established", there is no possibility of doing so from the data has been submitted. Useful information has been submitted and the pediatric section of labeling can be updated and improved.

The following can be added to labeling. Therefore, this is an "approvable" action.

Replace current Pediatric Use with:

Pediatric Use

Safety and effectiveness in children have not been established. The clearance of dopamine is affected by age (as much 2 fold greater in children under 2 years of age), renal and hepatic function (decreasing by 2 fold in the presence of either). In younger children, particularly neonates, clearance is highly variable. Newborn infants may be more sensitive to the vasoconstrictive effects of dopamine.

Draft Labeling

Draft Labeling

Add to Dosing and Administration. This should follow the current last sentence that reads "Drug additives should not be mqde to Dopamine Hydrochloride and 5% Dextrose Injection, USP.

Pediatric Dosing and Administration

In publications, the most common **starting** doses were 1-5 micrograms/kilogram/minute. **Particularly in neonates, such low doses require considerable dilution of this product; careful consideration should be given to the use of this product in such circumstances.** Dosing increments that were reported ranged from 2.5 to 5.0 micrograms/kilogram/minute. Usual maximum doses were 15-20 micrograms/kilogram/minute, with occasional use as great as 50 micrograms/kilogram/minute. The time course of dopamine kinetics are poorly defined. Increasing infusion rates (or dose) should be approached cautiously and only after it is apparent that hemodynamics (mainly systolic blood pressure0 have stabilized with respect the current dose and or rate of infusion.

APPEARS THIS WAY
ON ORIGINAL

BUEHLER

JUL 16 1999

Division of Cardio-Renal Drug Products
Medical Officer Review

NDA19, 615 (reference 012)

Name of Drug: Dopamine Hydrochloride and 5% Dextrose injection USP at 0.8, 1.6 and 3.2 mg/ml

Reviewer: Abraham Karkowsky 7/15/99

Date of Review: July 2, 1999

Summary:

The sponsor proposed to alter the labeling of dopamine hydrochloride infusion as follows:

Under WARNINGS:

The statement is to be added:

Under PRECAUTIONS, subsection pediatric use:

The sponsor proposes to delete the statement:

The sponsor proposes to insert the following:

The sponsor proposes to add the following under DOSAGE AND ADMINISTRATION

In support of these changes, the sponsor performed a literature search by searching Medline for the years 1966 through February 1997 and the International Pharmaceutical Abstracts from the years 1970 through February 1997. A total of 57 articles were identified, thirty-one of these articles were submitted. The articles are summarized below. The number corresponds to the tab number in the submission. My analysis of these papers follows a summary of these papers.

1. Allen, E; Pettigrew, A; Frank, D; Thompson, S; Myers, C; Yamashita, T and Blumer, JL; " Alterations in dopamine clearance and catechol-O-methyl transferase activity by dopamine infusions in children" Crit Care Med; 1997; 25, 91, 181-9.

Summary: The clearance and mononuclear-COMT levels were assessed for 14 dopamine-treated patients and five untreated controls. The ages of the children ranged for 16 days to 12 years. The doses ranged from 3 to 20 ug/kg/min. There was age and concentration-related differences in clearance for dopamine that did not correlated with COMT levels.

4. Hentschel, R; Hensel, D; Brune, T; Rabe, H and Jorch, G; "Impact on blood pressure and intestinal perfusion of dobutamine or dopamine in hypotensive preterm infants" Biol Neonate; 1995; 68 (5): 318-324.

Summary: There were 20 pre-term infants enrolled with arterial hypotension who received either dobutamine or dopamine (10 ug/kg/min). Blood pressure increased in both groups (more in the dobutamine group 8.3 versus 6.7 mm Hg). Both treatments also increased intestinal blood flow.

9. Zenk, KE; Noerr, B and Ward, R; "Severe sequelae from umbilical artery catheter administration of dopamine" 1994; Neonatal Netw, 13 (5) 89-91.

Summary: These are two adverse events reports in which dopamine was administered by catheter via umbilical artery instead of umbilical vein. The adverse events included excessive peripheral vasoconstriction. For one of these children, phentolamine was infused that reversed the vasoconstriction over several hours (comment: The time course required for phentolamine to reverse the vasoconstrictive effects i.e. hours does not appear to be consistent with the hemodynamic effects expected for dopamine).

10. Van Den Berghe, G; De Zegher, F and Lauwers, P " Dopamine suppresses pituitary function in infants and children" 1994; Crit Care Med: 23 (11) 1747-53.

Summary: A total of 33 children from the ages of 12 days to 6.7 years, who were recovering form cardiovascular surgery, received intravenous dopamine (5 ug/kg/min). Patients were stratified as either young (< 90 days) or older (>3months –6.7 years). Prolactin and thyrotropin was suppressed in both the young and older group of patients. Growth hormone was suppressed only in the younger patients.

12 Seri, I; Rudas,G; Bors, Z; Kanyicska, B; Tulassay, T; " Effects of low-dose dopamine infusion on cardiovascular and renal function, cerebral blood flow, and plasma catecholamine levels in sick preterm neonates" ; 1993; Pediatr Res; 34 (6) 742-9

Summary: A total of 41 sick preterm or term neonates received dopamine at either doses of 2 ug/kg/min (n=31) or some fraction (?) of whom also received 4 ug/kg/min (n=10) during the first 4 days of life. A group of sick normotensive neonates served as control for some measurements. Compared to pre-treatment, blood pressure increased on the 2-ug/kg/min-infusion dose and further increased at the 4-ug/kg/min dose. Pressor responses at low dose infusions suggest either an enhanced alpha-adrenergic sensitivity in this population and /or a decreased clearance of dopamine in this group (more in preterm than in term infants, but still evident in term infants). Cerebral blood flow paralleled blood pressure. Based on the low dose response of blood pressure, the authors posit that alpha-adrenergic effects are present at lower infusion rates in both premature and mature sick infants.

Diuresis and natriuresis were maximal on 2 ug/kg/min and did not increase at the 4-ug/kg/min-infusion rate.

Plasma dopamine concentrations in pre-term infants was more than double that observed in children (mean age 9.2 years) who received the same infusion rate (2 ug/kg/min).

Comment: The publication was confusing. I could not tell if those who received the 4 ug/kg/min were a subset of those who were treated with 2 ug/kg/min. It is also unclear what constituted baseline for renal function. Since the patients were treated with colloid prior to the start of the infusion any changes in renal function are likely the result both from the use of colloid and of dopamine treatment.

13. De Zegher, F; Van Den Berghe, G; Delieger, H; Eggermont, E and Veldhuis, J D;" Dopamine inhibits growth hormone and prolactin secretion in the human newborn" 1993; Pediatr Res; 34 (5) 642-5.

Summary: Growth hormone and prolactin levels were decreased in five infants undergoing exchange transfusion for polycythemia and who were treated dopamine. Recovery of growth hormone and prolactin rebounded within 2 hours after cessation of dopamine.

14. Greenough, A. and Emery, EF; " Randomized trial comparing dopamine and dobutamine in preterm infants" 1993; Eur J Pediatr 152 910 925-7.

Summary: A total of 20 hypotensive pre-term infants, unresponsive to colloid infusion received either dopamine or dobutamine at an initial dose of 5 ug/kg/min. Two upward titrations were allowed, one at 1 hour and the second at 2 hours after the start of the infusion. Blood pressure at three hours was higher in the dopamine than dobutamine groups.

15. Emery, EF and Greenough, A; "Efficacy of low-dose dopamine infusion" 1993; Acta Pediatr; 82, (5), 430-2.

Summary: Twenty sick preterm infants with anuria received low dose dopamine (starting at 3 ug/kg/min). Relative to the anuric period, urine output apparently mirrored increase in blood pressure.

Comment: This was a baseline-controlled study. During the first several days of life fluid is often mobilized from lungs and urine volume correspondingly, increases. The extent to which maturity, blood pressure or direct renal effects of dopamine increase urine flow is unclear.

17. Wenstone, R; Campbell, JM; Booker, PD and McKay, R; " Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine" 1991; Brit J Anaesth, 7 (5) : 591-594.

Summary: A total of 142 children younger than 10 years old who were undergoing cardio-pulmonary bypass were allocated to either dopamine or dobutamine (either at 2.5 ug/kg/min). There were no clinical or statistically significant differences between the two groups in postoperative urine output, serum concentration of creatinine, fractional sodium excretion or need for diuretic therapy.

19. Stopfkuchen, H; Racke, K; Schworer, H; Queiser-Luft, A and Vogel, K;" Effects of dopamine infusion on plasma catecholamines in preterm and term newborn infants" 1991; Eur J Pediatr, 150 (7) 503-6.

Summary: A total of 34 infants (21 preterm and 13 term) received dopamine infusions beginning at 2.5 to 3.4 ug/kg/min. Plasma catecholamines increased in an apparent dose related manner.

20. Cuevas, L; Yeh, TF; John, EG; Cuevas, D and Plides, RS; "The effect of low-dose dopamine infusion on cardiopulmonary and renal status in premature newborns with respiratory distress syndrome"; 1991, Am J Dis Child: 145 (7), 799-803.

Summary: A total of 60 premature infants with respiratory distress syndrome were randomized to receive either no dopamine (n=20); dopamine at 1 ug/kg/min (n=20) or dopamine at 2.5 ug/kg/min (n=20). Of these children, four died (2 on control, 1 each on the two dopamine infusion rates) and seven patients discontinued due to blanching (all in the dopamine groups). There were, therefore, 18 patients in the control group; 16 in the 1 ug/kg/min group and 15 in the 2.5 ug/kg/min group for which data was available. Among the three groups there were no differences in ventilation or blood pressure during three days of observation. The 1-ug/kg/min dose but not the 2.5-ug/kg/min increased fractional excretion of sodium and urine osmolarity clearance relative to control. The 2.5-ug/kg/min actually had numerically lower values than control.

21. Outwater, KM; Treves, T; Lang, P; Casteneda, AR and Crone, RK; "Renal and hemodynamic effects of dopamine in infants following cardiac surgery" 1990: J Clin Anaesth, 2 (4) 253-7.

Summary: This was a baseline (post surgery) controlled study in six patients between the ages of 3-13 months who received dopamine status post repair of congenital heart defects. At 4- hour intervals doses of dopamine were increased from 5 to 10 to 15 ug/kg/min.

27. Notterman, DA; Greenwald, BM; Moran, F; Dimaio-Hunter, A; Metakis, L and Reidenberg, MM; " Dopamine clearance in critically ill infants and children: effect of age and organ system dysfunction" 1990: Clin Pharmacol Ther, 48 (2): 138-17.

Summary: A total of 27 acutely ill patients between the ages of 2 days and 18 years received constant infusions of dopamine. The most common reason for initiating dopamine was septic shock. Of the 27 subjects, twelve died. Clearance of dopamine was measured in all these patients. There was a negative correlation between age and dopamine clearance. Clearance of dopamine was diminished in children with both hepatic and renal dysfunction.

29. Miall-Allen, V and Whittelaw, AGL;" Response to dopamine and dobutamine in the preterm infant less than 30 weeks gestation" 1989; Crit Care Med; 17 (11): 1166-9.

Summary: A total of 12 preterm neonates who received dopamine (starting at a 5 ug/kg/min) for hypotension, unresponsive to volume expanders. In non-responders, dopamine could be increased to 10 ug/kg/min and if necessary, dobutamine at 10 ug/kg/min could be added. These changes could be implemented after 90-minute intervals. Non-response was defined of a MAP of less than 30 mm Hg. There were differences among those classified retrospectively as responders (n=5) and non-responders (n=7).

30. Seri, I; Hadju, J; Kiszel, J; Tullasay, T and Aoperia, A; " Effect of low-dose dopamine infusion on urinary prostaglandin E2 excretion in sick, preterm infants"; 1988; Eur J Pediatr, 147 (6): 616-20.

Summary: Urinary PGE2 levels were measured in a total of 6 preterm infants who required dopamine for edema, moderate oliguria, poor peripheral perfusion and/or mild hypotension. The dose of dopamine was 2-ug/kg/min.

31. Tullasay, T; Rascher, W; Hajdu. J; Lang, RE; Toth, M; and Seri, I; "Influence of dopamine on atrial natriuretic peptide level in premature infants"; 1987, Acta Pediatr Scand, 76, 910 42-46.

Summary: Dopamine starting at a dose of 2 ug/kg/min to eleven premature infants did not alter atrial natriuretic peptide levels.

34. Seri, I; Tulassay, T; Kiszel, J; Ruppert, F; Sulyok, E; Ertl, T; Bodis, T and Cosmor, S; " Effect of low-dose dopamine infusion on prolactin and thyrotropin secretion in preterm infants with hyaline membrane disease"; 1985, Biol Neonate, 47 (6): 317-322.

Summary: Low dose dopamine (2-4 ug/kg/min) decreased both thyrotropin and prolactin from pre-infusion levels.

35. Seri, I; Tulasay.T. et al;" The use of dopamine for the prevention of the renal side effects of indomethacin in premature infants with patent ductus arteriosus" 1984; Int J Pediatr Nephrology.

Summary: Sixteen preterm infants who had PDAs, and were to be treated with indomethacin (at a dose of 0.3 mg/kg), were randomized to receive either dopamine at a dose of 2 or 4 ug/kg/min (n=5 and n=3, respectively) or no treatment (n=7). Indomethacin treatment altered renal dynamics. Those who received dopamine in conjunction with the indomethacin had higher urinary volume, sodium clearance, osmolar clearance and fractional excretion of sodium during the 24-hour period after indomethacin treatment than those who received placebo

36 Venkataraman, PS; Babcock, DS; Tsang, RC and Ballard, JL; " Hepatic injury: a possible complication of dopamine infusion through an inappropriately placed umbilical catheter"; 1984;. Am J Pernatol. 1 (4) : 351-4

Summary: A preterm infant, who received dopamine via an umbilical venous catheter, had liver damage, presumably because the catheter was placed in the portal vein.

37 Koerber, RK; Haven, GY; Cohen, SM; Fleming, WH; and Hofschire, PJ; "Peripheral gangrene associated with dopamine infusion in a child"; 1984; Clin Pediatr, 23 (2), 106-7

Summary: A child developed peripheral gangrene after treatment with modest doses of intravenous dopamine (4-9 ug/kg/min).

39. Seri, I; Tulassay, T; Kiszel, J; Machay, T; and Csomor, S; " Cardiovascular response to dopamine in hypotensive preterm neonates with severe hyaline membrane disease";1984; Eur J Pediatr ,142 (1): 3-9.

Summary: This study collected changes in blood pressure and heart rate compared to baseline in a cohort of hypotensive, premature infants with hyaline membrane disease. Dopamine was administered to this cohort at doses of between 2- to 8-ug/kg/min. The sponsor notes that tachycardia was only obvious among those who received 8 ug/kg/min dose. Mortality occurred in 50% (9/18) patients who were part of this cohort.

42. Maggi, JC; Angelais, J. and Scott, JP; " Gangrene in a neonate following dopamine therapy"; 1982; J Pediatr, 100 (2), 323-325

Summary: This was a patient who received dopamine infusions through an intravenous foot line, starting at 7 ug/kg/min and subsequently decreased to 5 ug/kg/min, who developed peripheral gangrene with loss of several toes.

44. Fiddler, GI; Chatrath, R; Williams, GJ; Walker, DR; Scott, O;" Dopamine infusion for the treatment of myocardial dysfunction associated with a persistent transitional circulation"; 1980; Arch Dis Child 55 (3) 194-8.

Summary: Four patients, with persistent transitional circulation, clinically responded to low dose dopamine 2-5 ug/kg/min.

47. Disessa, TG; Leitner, M; Ti, CC; Gluck, L; Coen, R and Friedman, WF;" The cardiovascular effects of dopamine in the severely asphyxiated neonate"; 1981; J Pediatr 99 (5); 772-776

Summary: This was a small placebo-controlled study in which 14 full term infants with asphyxia were randomized to either placebo or dopamine at a dose of 2.5 ug/kg/min. Of several parameters measured only systolic blood pressure difference after treatments. Diastolic blood pressure as well as several parameters, reflective of cardiac performance, was numerically but not statistically increased. There were two deaths in the placebo and no deaths in the dopamine cohort. Two additional placebo patients had evidence of anoxic CNS damage. For the dopamine group three patients had evidence of anoxic CNS damage.

51. Lang, P; Williams, G; Norwood, WI; Casteneda, AR; " The hemodynamic effects of dopamine in infants after corrective cardiac surgery"; 1980; J Pediatr, 96 (4), 630-4.

Summary: The hemodynamics (baseline-controlled) in 5 post-cardiac surgery patients, less than 2 years old, who received doses of dopamine of 5, 10, 15, 20 and 25 ug/kg/min were measured. Hemodynamic effects i.e. heart rate, MAP and CI were convincingly increased only at doses of > 15 ug/kg/min.

52. Girardin, E; Berner, M; Rouge, JC; Rivest, RW; Friedli, B; Paunier, L; " Effect of low dose dopamine on hemodynamic and renal function in children"; 1989, Pediatr Res; 26 (3), 200-3.

Summary: This was a baseline-controlled study of hemodynamics and renal function in a total of 14 patients between the ages of 18 months and 15 years who were status post cardiac surgery. Patients

received either 2.5 or 5 ug/kg/min of dopamine (randomly assigned) for one hour then the alternate infusion rate. Compared to baseline, there were increases in measurements of renal function that appeared dose related. Cardiac index also appeared to be increased in a dose-related fashion. There did not appear to be statistical differences between the two highest doses.

Comment: Although the effects of the dopamine doses were clearly different from baseline, the two randomized doses do not appear to be statistically different.

53. Perez, CA; Reimer, JM; Schreiber, MD; Warburton, D; Gregory. GA; " Effects of dopamine on urine output in newborn infants"; 1986, Crit Care Med, 14 (12), 104-9

Summary: The data include 15 newborn term infants; five studied prospectively and 10 retrospectively. Patients were started at a 5 ug/kg/min dose of dopamine, but were rapidly up-titrated every 5 to 10 minutes in order to achieve a MAP corresponding to a capillary fill time of < 2 seconds. Urine output recorded for the 2 hours prior to infusion served as baseline. Compared to baseline measurements, urine output, MAP and heart rate all increased. Two of 15 patients who received high dose dopamine died.

54. Roze, JC; Tohier, C; Mainguenerau, C; Lefevre, M; Mouzard, A; " Response to dobutamine and dopamine in the hypotensive very preterm infant"; 1993; Arch Dis Child, 69 (1), 59-53.

Summary: This study was carried out in a cohort of hypotensive preterm infants (< 32 weeks gestation, n=20). The initial starting dose was 5 ug/kg/min of either dobutamine or dopamine. If the MAP was less than 31 mm Hg, the dose was sequentially increased at 5 ug/kg/min increments, with a maximal dose of 20 ug/kg/min. If the original drug was incapable of raising blood pressure to > 31 mm Hg, the infant was switched to the alternate treatment.

Six of the 10 patients who received dobutamine did not respond adequately with increases in MAP and were switched to dopamine. Left ventricular output, however, was increased on dobutamine but decreased on dopamine.

55. Seri, I; Tulassay, T; Kiszel, J; Sulyok, E; Ertl, T; Bodis, J; Csomor, S; " Effect or low-dose dopamine on catecholamine values in cerebrospinal fluid in preterm neonates"; 1984; J Pediatr; 105 (2), 489-91.

Summary: This was a study on the effect of dopamine at a rate of 1-4 ug/kg/min on CSF dopamine and noradrenaline. There were increases in both catecholamines after dopamine infusion.

56 Zaritsky, A; Lotze, A; Stull. R; Goldstein, DS;" Steady-state dopamine clearance in critically ill infants and children"; 1988; Crit Care Med; 16; 217-220.

Summary: This study examined steady state kinetics of dopamine in preterm and term infants as well as pediatric patients (usually post cardiovascular surgery). The dopamine infusion rate ranged from 0.57 ug/kg/min to 11ug/kg/min. Clearances were extremely variable. The concentrations of dopamine varied by a factor of approximately 10^5.

57. Sulyok, E; Tullasay, T; Kiszel, J; Ertl, T; "The effect of dopamine administration on the activity of the renin-angiotensin-aldosterone system in sick pre-term infants"; 1985; Eur J Pediatr, 143: 191-193

Summary: Dopamine was administered to sick preterm infants at a dose of 2-4 ug/kg/min. There was baseline-controlled data for blood pressures and urine output. Systolic blood pressure was increased, diastolic actually decreased and urine output and sodium clearance increased.

Reviewer's Analysis:

Based on these papers I do not agree with the changes offered by the sponsor. Below is my analysis of the submitted papers.

1. Kinetics:

The kinetics of dopamine appear to be highly variable in critically ill infants (preterm and mature) and children (article#1, # 12, #27, # 56,). In at least one study, the steady state levels versus infusion rate appear non-linear, hyperbolic upward (#1). In one study (#56), there did not appear to be any relationship between infusion rate and plasma concentration. In one study the concentrations of dopamine after long term infusion in premature infants was about 2-fold those in children (# 12). The clearance of dopamine in younger children appear greater than those younger than 2-years (age > 2 days) when compared to those older than 2-years (#27). Others, however, found post-natal age did not correlate with dopamine clearance (# 56). Dopamine clearance among those with hepatic dysfunction (as judged by elevated conjugated bilirubin > 0.9 mg/dl), was decreased (#27, #56).

2. Dose range studied

There is heterogeneity in starting doses for infusion. Doses as low as 0.57 ug/kg/min have been used. The more frequent initial doses used was 2 to 5 ug/kg/min.

There was no data on the time dependent kinetics of dopamine in either premature, mature infants or in children. Consequently, there is no guidance as to how frequently to alter infusion rates. There was enormous heterogeneity as to how frequently dopamine infusion rates were increased. In most studies, infusion rates were allowed to stabilize over one to several hours. Often the reason for the long duration between upward titration was for the performance of specific measurements, and to assure that such measurements reflect steady state concentrations. Two studies increased infusion regimens at 10-minute intervals (# 51, # 53). However, only 5 patients were so treated and there was no specific safety assessment included as part of the study

The maximum dose that I saw was 435 ug/kg/min (sic), with 9 subjects treated with maximal infusion of greater than 50 ug/kg/min (#53). Other studies generally stopped at infusion rate of 20-25 ug/kg/min (# 51, # 54)

3. Mechanism of Action

The mechanism by which dopamine putatively works in adults is through interaction with dopamine, $beta_1$-adrenergic and alpha- adrenergic receptors and also by displacing catcholes from nerve endings. In adults there is some separation of the sensitivity of the various receptors with infusion rate, with dopamine receptors activated initially followed by $beta_1$-adrenergic receptors and at still higher doses alpha-adrenergic receptors. There is some information that alpha- adrenergic receptor effects may be more active in young children.

4. Efficacy:

None of the studies are sufficiently powered to address either a mortality benefit of morbidity benefit for dopamine among infants or children. A large number of the studies, however, assessed either hemodynamic (blood pressure or heat rate) or renal function. Most of the studies, however, were baseline controlled or utilized some non-randomized control group. There were, however, seven studies for which either placebo, positive control groups or were dose ranging. These studies are summarized in the table below.

A note of caution, the studies are small and consequently any study which does not demonstrate an anticipated dopamine effect, might reflect the diminished power of such small studies to detect these effects. Conversely, the small studies generally amplify any publication biases, with only studies having positive results, submitted for review and publication.

Dopamine appears to consistently increase systolic blood pressure and mean arterial pressure (this may be solely related to the increase in systolic blood pressures). There is little data that adequately define the effects of dopamine on heart rate. In at least one study (# 54) there was a decrease in left ventricular outflow in patients who received between 5-20 ug/kg/min of dopamine when compared to titrated dobutamine. For dopamine, not only was left ventricular outflow less than dobutamine, but it appeared to be diminished from baseline by approximately 16%. The decrease in outflow suggests that the $beta_1$-adrenergic effect is muted in this population of preemies.

Aside from the effect of dopamine on maintaining renal function in patients who receive indomethacin, there is little convincing or reproducible data (or internally consistent data) that dopamine alters renal function. In the largest of the submitted studies, among more than 140 patients randomized to dopamine or dobutamine, no reproducible effect on renal function was evident.

Table 1. Summary of controlled hemodynamic studies.

Article #	Population	Number Enrolled	Control	Parameter	Conclusion	Comments
4	Hypotensive premature infants	DA 10 ug/kg/min n=10	DBT 10 ug/kg/min n=10	MAP, HR, Vm	Both treatments↑ MAP	Both treatments apparently increase HR
14	Hypotensive preterm infants	DA= 5-15 ug/kg/min (titration) n=20	DBT 5-15 ug/kg/min (titration) n=20	BP	Mean BP at the end of 1 hour (all receiving 5 ug/kg/min) and at 3 hours showed ↑BP with DA	Heart rate not reported.
17	Post surgery children (5 weeks to 9 years)	DA 2.5 ug/kg/min n=74	DBT 2.5 ug/kg/min n=68	Urine output	No differences between low dose DA and DBT	No comments on BP or HR
20	Premature infants with RDS	DA 1ug/kg/min n=16 DA 2.5 ug/kg/min n=15	No DA treatment n=18	Renal parameters	Only fractional excretion of sodium in the 1 ug/kg/min differed from control. The 2.5 ug/kg/min showed no effect.	Not very convincing given the multiplicity of parameters and absence of dose-response effect
35	Premature Infants that are to receive indomethacin	DA 2-4 ug/kg/min n=8	no DA n=7	Renal parameters	Urine volume, sodium clearance, osmolar clearance and fractional excretion of sodium preserved in those infants taking indomethacin relative to placebo patients.	Systolic but not diastolic blood pressures were also increased. I could find no comments on HR.
47	Asphyxiated neonates	DA 2.5 ug/kg/min n=7	PBO n=7	Systolic/diastolic blood pressure an % fractional shortening and Vcf	Systolic blood pressure ↑	Though diastolic blood pressure and fractional shortening trended to increases (NS). HR apparently not statistically ↑
54	Hypotensive Very Preterm Infants	DA 5 - 20 ug/kg/min via titration n=10	DBT 5-20 ug/kg/min via titration n=10	MAP, LVO, SVR	MAP ↑on DA LVO ↓on DA SVR ↑on DA	At these doses DA has less beta effect and more $alpha_1$ effects

DA= dopamine DBT=dobutamine MAP=mean arterial pressure HR= heart rate Vm max flow velocity superior mesenteric artery Vcf= Velocity of Circumferential Fiber Shortening RDS= respiratory distress syndrome LVO-left ventricular outflow SVR-Systemic Vascular Resistance NS-not-statistically

5. Safety:

The sponsor tabulates a total of 710 patients exposed either to dopamine or control in this database, of which 516 were exposed to dopamine (my count). The safety of dopamine in any of the populations and at any of the doses is poorly described in the papers. In general, the studies were too small and the populations sufficiently sick that any adverse outcomes or lack of adverse events are not interpretable. Important concerns, such as the frequency of rhythm alterations, can not be teased out from these publications.

The only novel safety issue that is unique to the pediatric population is the infusion of dopamine through novel portals i.e. the umbilical artery or umbilical venous catheters. At least one paper (# 9) contains adverse sequelae in 2 patients who received dopamine via an umbilical artery catheter. The infusion rate of dopamine was not stated. A second paper (# 36) describes the outcome of an infusion in which the catheter was placed so that dopamine was infused into the portal system. Again, the infusion rate was not stated. Two additional papers (#37, #42) describe peripheral gangrene in single patients who received modest does of dopamine (4-9 ug/kg/min). Other studies (several) routinely infused dopamine through umbilical artery catheters.

The concentrations of dopamine in this particular product are not appropriate for most infants and small children. Consider a 1-kg child who is to be treated with an infusion of 2 ug/kg/min. Over 1 hour this child would receive a total of 120 ug/kg/hr. Since the lowest concentration of this product is 800 ug/ml, this child would of necessity receive 0.15 ml/hr, far too little for accurate delivery by most pumps. The sponsor is, therefore, correct to include within labeling the cautionary note that other preparations of dopamine may be more appropriate.

6. Conclusions:

The kinetics (time-dependent onset and offset kinetics) of dopamine in premature, full term infants as well as in children have not been adequately explored. The only information that is available is clearance data during longer term and presumably steady state levels of dopamine. The concentrations in these populations were highly variable, but may reflect a decrease in clearance in several of these pediatric populations. Instructions for use, such as the initial dose as well as the duration of time prior to altering the dose, if based on the current labeling of adults may result in excessive concentrations in pediatric patients. Dosing adjustment, should therefore, be made only if hemodynamics have stabilized. The initial dose in pediatrics should also reflect the lack of information as to equivalence with adult effects.

Although it is clear that dopamine has hemodynamic effects and likely renal effects, there is no paper that demonstrates a clinical benefit of using dopamine (at low doses) in any population. In the largest of the studies (#17) dopamine did not differ in altering renal parameters in patients post surgery than did dobutamine. Dopamine is a putative renal dilator, due its direct effects; dobutamine should not. Dopamine in premature patients who received indomethacin, however, maintained renal function to a better extent than those who received no dopamine therapy. None of the patients either treated with dopamine or controls sustained a renal shutdown.

With respect to hemodynamics, there is evidence that dopamine increases blood pressure but it is unclear if this represents an alpha-adrenergic agonist or beta1-agonist activity. Dopamine, however, seems to decrease left ventricular outflow in hypotensive extreme premature infants. The decrease in outflow seems incongruous with a substantial beta-$_1$ adrenergic effect. There are, in addition, several case reports of profound peripheral vasoconstriction at modest doses of dopamine, that suggest alpha-1 agonistic activity is more prominent in infants than it is in adults. Although dopamine is hemodynamically active, the particular spectrum of activity is not well established. Both the age-dependent density of the various receptors (i.e. alpha-adrenergic, beta$_1$-adrenergic and dopamine) on the vasculature of various organs as well as the efficiency of coupling of this binding to intracellular mediators of effect, may differ in pediatric and adult patients.

Labeling Comments:

I would like to suggest changing the pediatric section, as follows:

Pediatric use:

WARNING:

Draft Labeling

Draft Labeling

Under DOSING AND ADMINISTRATION

DRAFT LABELING

cc NDA 19,615
HFD-110 CSO/FILE/AKarkowsky

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-615/S-012

CHEMISTRY REVIEW(S)

Cunningham

JUN 30 1999

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-615
3. Name and Address of Applicant (City & State) Baxter Healthcare Corporation Route 120 & Wilson Road Round Lake, IL 60073		4. Supplement(s) Number(s) Date(s) ~~SLR~~-012 6/22/99 SE5
5. Drug Name Dopamine HCl in 5% Dextrose in Plastic Container PL 2207	6. Nonproprietary Name Dopamine hydrochloride Dextrose	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Pediatric labeling.		
9. Pharmacological Category Correction of hemodynamic imbalance present in shock	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 0.8mg/mL, 1.6mg/mL 3.2mg/mL, 6.4mg/mL	
14. Chemical Name and Structure 3,4-dihydroxyphenetylamine hydrochloride and D-glucopyranose monohydrate		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Changes are in pediatric use. Supporting documentation is included.

Mark-up copy of current labeling is also included.

Insert - 7-19-4-933 Rev. April 1999 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.

17. Conclusions and Recommendations:

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER		
Name Danute G. Cunningham	Signature /S/	Date Completed June 29, 1999

Distribution: ☐ Original Jacket ☒ Reviewer ☐ Division File ☐ CSO

19615S12.SUP

/S/
6-29-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-615/S-012

PHARMACOLOGY/TOX REVIEW(S)

NDA 19-615

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

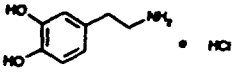
KEY WORDS:
DOPAMINE, PEDIATRIC LABELING

Estela A. Gonzalez Barry, M.S.
Division of Cardio-Renal Drug Products

Review Completion Date: 08-04-99
Review Number: 1
Type of Document/Submission Date: Supplemental Application in response to "Pediatric Use" Subsection in the Labeling: Final Rule dated 12-13-94 59 **FR** 64240-64250)
Center/Division Receipt Date: 06-24-99

Sponsor: Baxter Healthcare Corporation, Round Lake, Illinois 60073
Manufacturer for Drug Substance: Not reported.

Drug:
Code Name: ASL-279
Generic Name: Dopamine Hydrochloride and 5% Dextrose.
Trade Name: Dopamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container Viaflex Plus Container.
Proprietary Name: **None**
Chemical Names of Active Ingredient:
4-(2-aminoethyl)-hydrochloride 1,2-benzenediol hydrochloride;
4-(2-aminoethyl)pyrocatechol hydrochloride
3-hydroxytyramine for the free base.
CAS Registry Names: CAS 51-61-6 for dopamine and,
CAS 62-31-7 for the hydrochloride.
Molecular Formula/Molecular Weight:

MW 189.64 

Relevant DMF: None found.

Drug Class: Catecholamine.
Therapeutic Indication: Sympathomimetic agent.
Clinical Formulation/Route of Administration: Dopamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container Viaflex containing 0.8, 1.6 or 3.2 mg/Ml of the active ingredient is marketed by Baxter Healthcare Corporation for intravenous (iv) infusion. The drug is indicated for "...**for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure and chronic cardiac decompensation as in congestive failure.**"

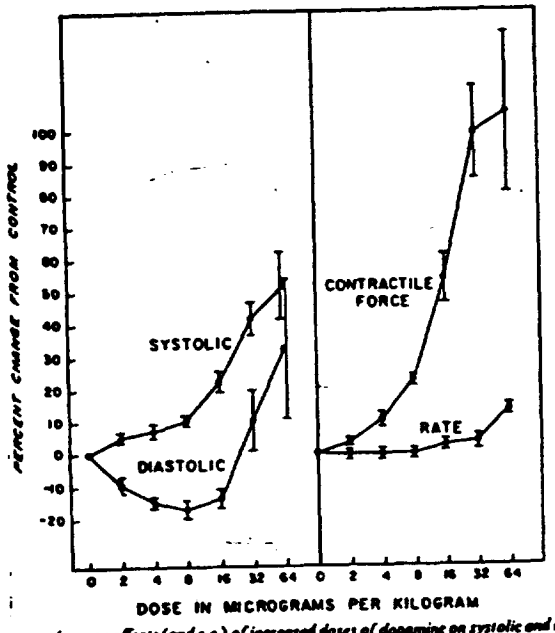
The presently approved label for this drug product states under the subsection **Indications and Usage**, that it is used in cases of poor perfusion of vital organs, low cardiac output and, hypotension.

Previous Clinical Experience: Dopamine is inactive by oral route and dopamine solutions have been approved/marketed for iv use for many years.

<.....>

INTRODUCTION and HISTORY OF DOPAMINE: Briefly, the literature reports that in 1910 Sir H. Dale described basic relationships between chemical structure and adrenergic activity. H. Blaschko reported the correct byosynthetic pathway of catecholamines starting from tyrosine ~ 1939. In the 1940s, P. Holtz reported on dopadecarboxylase and the vasodilating action of **dopamine**. In the 1950s L. Goldberg studied dopamine because a biochemist had asked him to differentiate its actions from NE.

To differentiate dopamine from NE, the investigators used the open-chest **dog** preparation for direct estimation of the inotropic contraction of the heart (using a strain-gauge arch); heart rate (**HR**) and blood pressure (**BP**) was also measured. The author reported that dopamine at low conc (~ 2 μg/kg iv) reduced the diastolic pressure (reduction was not blocked by ß-blockers), and caused no change in HR and a slight increase in cardiac contractility. At higher doses of dopamine (~ 8 μg/kg iv), the diastolic/systolic pressure, contractile force started to rise (these actions were later found to be due to an α-adrenergic effect of dopamine resembling the action of NE). When the dose of dopamine was increased to 32 μg/kg iv, the HR started to increase*.



Average effects (and s.e.) of increased doses of dopamine on systolic and diastolic blood pressure and on heart rate and contractile force in 16 anaesthetized dogs (McDonald & Goldberg 1963).
(Reproduced by permission of Journal of Pharmacology and Experimental Therapeutics)

* Goldberg, et al in "The Pharmacological Basis of the Clinical Use of Dopamine": Proc Royal Soc of Med: V. 70(2):7-15, 1970.

Since the response to dopamine in normal human subjects were found to be similar to those in **anesthetized dogs**, it was decided to also study the drug in patients with congestive heart failure (**CHF**) considering that if dopamine could increase cardiac output (**CO**) without increasing peripheral resistance or altering HR, then the drug might be expected to be beneficial in the treatment of **CHF**. The literature later reported clinical studies in CHF patients in which the effectiveness of infused dopamine, at different rates/conc, did not change arterial BP or HR but increased cardiac index, and Na^+ excretion and, renal blood flow (indicating a decrease in vascular resistance).

Following the demonstrated efficacy of dopamine in CHF, studies were also conducted investigating the drug in the treatment of shock-like states (condition characterized by inadequate perfusion of tissues and hypotension). At that time of these studies, the drug of choice in the treatment of shock-like states was isoproterenol.

Dog studies were conducted comparing isoproterenol to dopamine on renal blood flow, BP and cardiac contractile force; the results showed that the two drugs had about the same effects on BP and cardiac contractile force. However, dopamine was found to promote dilatation splanchnic vascular bed and renal arterial dilatation (thus preserving renal function) and at higher doses activating adrenergic receptors causing peripheral and renal vasoconstriction; isoproterenol did not increase renal blood flow (by diverting blood flow to the skeletal muscle, and mesenteric vascular bed).

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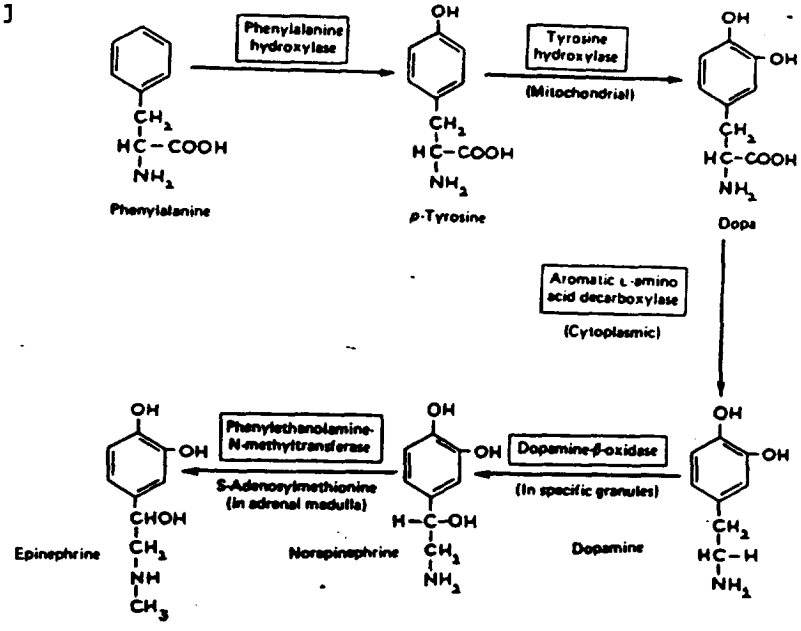
ON ORIGINAL

>> **NONCLINICAL STUDIES SUBMITTED IN THIS SUPPLEMENTAL NDA**: None.

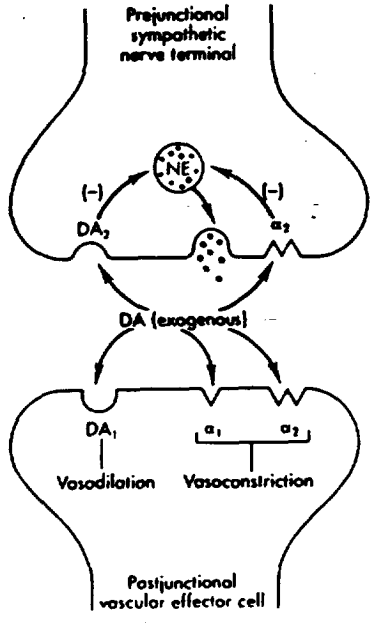
♦ **PHARMACOLOGY** (Published information): The accepted biosynthetic pathway of dopamine is depicted below. Fig. 1 shows that in the the amino acid phenylalanine is hydroxylated to tyrosine; tyrosine is hydroxylated to 3,4-dihydroxyphenylamine (**DOPA**); DOPA is then decarboxylated to form the catecholamine **dopamine**. Dopamine is rapidly converted by the enzyme ß-hydroxylase to norepinephrine (**NE**), the natural precursor of epinephrine (**E**).

Fig 1



Mechanism of Action/Activity Related to Proposed Indication:

One physiologic action of dopamine is to release of **NE** from the stores in sympathetic nerve endings of the heart. The cardiovascular effects of dopamine are mediated through several different types of receptors. In mammals two classes of dopamine receptors (DA_1 and DA_2) have been identified and, at least 2 and 3 different subtypes, respectively, have been characterized.



Location of the subtypes of dopamine and α-receptors. DA_1 receptors, α_1-receptors, and α_2-receptors are located on postganglionic vascular effector cells and DA_2 receptors are on the prejunctional sympathetic nerve terminal. With dopamine infusion, activation of DA_1 receptors causes vasodilation and activation of DA_2 receptors causes inhibition of norepinephrine (NE) release. A higher dose of dopamine simulates α_1- and α_2-receptors on the effector cells to cause vasoconstriction and prejunctional α_2-receptors to inhibit release of norepinephrine. (Modified from Goldberg LI, Rasfers SI: Dopamine receptors: Applications in clinical cardiology. Circulation 72:245, 1985. Reprinted with permission of the American Heart Association, Inc)

The action of dopamine on the heart is overridden in the periphery by the activity of dopamine, of the prejunctional dopaminergic **DA_2**-receptors, by inhibiting **NE** release and thereby causing vasodilation. The prejunctional **DA_1**-receptors cause direct vasodilation in renal, mesenteric, coronary and cerebral vascular beds.

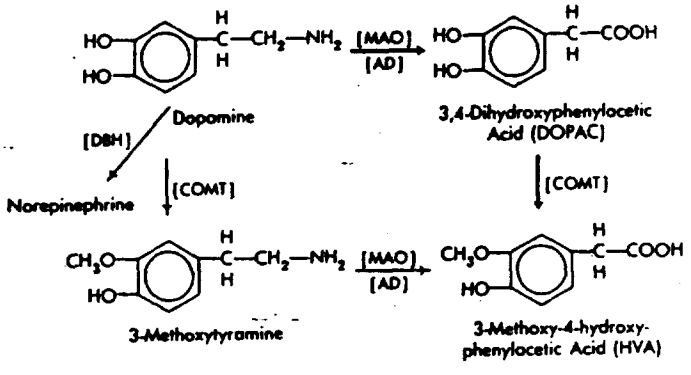
As noted in Fig. 1 above, dopamine is a substrate for both the enzymes monoamine oxidase (**MAO**), a flavoprotein present in some organs, blood platelets and neuronal tissue and, catechol-O-methyltransferases (**COMT**), a cystosolic enzyme present in virtually in all tissues included erythrocytes with the highest conc found in the liver/kidney. Dopamine derivatives undergo sulfate conjugation.

Nonclinical reports indicate that at low conc, dopamine interacts with vascular receptors in the renal, mesenteric and coronary bed by activating adenylyl cyclase and raising intracellular conc of cyclic AMP resulting in vasodilation. Infusion of low doses of the drug causes an increase in glomerular filtration rate, renal blood flow and Na^+ excretion. Since dopamine releases NE from nerve terminals, at higher conc the drug exerts a positive inotropic effect on the heart acting via the ß1-adrenergic receptors.

♦ **SAFETY PHARMACOLOGY**: No studies were submitted and none are required for this approved/marketed drug.

♦ **NONCLINICAL PHARMACOKINETICS/TOXICOKINETICS**: No studies were submitted and none are required.

As stated above, dopamine is inactive by oral route. The drug is metabolized by the enzymes MAO and COMT, respectively to 3,4-dihydroxyphenylacetic acid (**DOPAC**) and 3-methoxytyramine.



Briefly, the literature also reports that in healthy [adult] males, after infusion of ^{14}C-dopamine (dose ?), ~ 75% of the dose was recovered as dopamine metabolites primarily excreted in the urine; the administered radioactive dose was quantitatively recovered within by 5 days. The principal metabolites of the drug reported were DOPAC and 3-methotyramine. Other metabolites identified in that report included 3,4-dihydrozyphenylethanol and 3-methoxy-4-hydroxyphenylethanol (no structures provided). The remaining 25% of the infused dopamine was said to be transformed into NE and appeared in the urine principally as metabolites of NE.*

One reference cited within the above journal article briefly stated that studies conducted with dopamine using in cultured human skin fibroblasts and rat hepatoma cell showed that the principal conjugates of dopamine were 3-O-sulphates and 3-O-glucuronides; no chemical structures for these metabolites were provided.**

* James E. Carter, et al, "Dopamine Hydrochloride" in Analytical Profiles of Drug Substances, v. 11:257, 1982.

** P.A. Crooks, et al, Biochem J, v. 176:187, 1978.

APPEARS THIS WAY
ON ORIGINAL

♦ **TOXICOLOGY**: No new studies were reported.

The presently approved label for this drug product addresses nonclinical studies under the section "**Precautions**." Results of an in depth literature search covering the last 5 years revealed reports indicating that among the naturally occurring catecholamines, dopamine is considered the most cytotoxic because of its ease of autoxidation.[1] Other reports on **in vitro** studies describe some of the cytotoxic properties of dopamine (e.g, as a source of free radicals,[2] a decreaser of the activity of superoxide dismutase and levels of glutathione in cloned catecholaminergic cell line-derived from the central nervous system,[3] an inducer of DNA damage through its oxidative metabolites,[4] etc.)

Reports of **in vivo** studies describe damage caused by dopamine, by a variety of mechanisms, on the arterial vasculature.[5] Studies in the Dept. of Pediatrics, Madigan Army Medical Center, Tacoma, WA reported that rabbits injected with dopamine (40 mg/kg by iv?) showed a decrease in plasma levels of the enzyme pyridoxal 5'-phosphate. (The conversion of DOPA to dopamine is catalyzed by the pyridoxine-dependent enzyme L-amino acid decarboxylase.[6]) When dopamine plus vitamin B6 was injected to the rabbits, there was an increase in the enzyme pyridoxal 5'-phosphate. The authors interpreted these findings as suggesting that dopamine may increase the requirements of the vitamin B6 and, were concerned about **drug interactions** when the drug is given with other drugs in the critical care settings, that could aggravate alterations in the body stores of vitamin B6, creating a deficiency.

In humans, the literature reports adverse reactions associated with infusion of dopamine include extravasation injuries resulting in tissue damage that later required complex treatments or interventions; unexpected reflex vasodepression; mydriasis gangrenous extremities, etc. The drug sponsor also provided a list of reports on human adverse findings reported in the literature.

1. Chapter XVI- "Toxic Responses of the Nervous System" by Douglas C. Anthony, et al, (p.469) in Casarett & Doull's Toxicology: The Basic Science of Poisons, McGraw-Hill, 1995.

2. Jacobson, S et al "Dopamine and glutamate neurotoxicity in cultured chick telencephalic cells: Effects of NMDA antagonists, antioxidants and MAO inhibitors," in Neurochem Int, v. 34(1):49, 1999.

3. Gong, L et al "Brain-derived and glial cell line-deprived neutrophic factors protect a catecholaminergic cell line from dopamine induced cell death," in Neurosc Lett, v 263:153, 1999.

4. Daily, D at al "The involvement of p53 in dopamine-induced apoptosis of cerebellar granule neurons and leukemic cell overexpressing p53" in Cell Mol Neurobiol, v 19(2):261, 1999.

5. Kerns, MD et al "Role of dopaminergic and adrenergic receptors in the pathogenesis of arterial lesions induced by fenoldopam mesylate and dopamine in rat" in Am J Pathol 135(2):339, 1989

6. Rats reared on B6 deficient diet show abnormally low levels of dopa decarboxylase activity. (H Blascho "Enzymology " Pharm Rev, v.18(1):39, 1966.)

♦ **CARCINOGENICITY**: Since dopamine is commonly administered by the iv route, its use is restricted to short-time treatment. Thus, no carcinogenicity studies were required.

♦ **REPRODUCTIVE TOXICOLOGY**: No new studies were reported and none are required.

The present label includes previously evaluated animal developmental toxicity studies in rats and rabbits treated with dopamine hydrochloride. In one rat study, the drug was administered subcutaneously (**sc**) and, in subsequent studies both rat and rabbits were treated with dopamine doses up to 6 mg/kg iv.

Results reported indicated that pregnant rats treated with dopamine **sc** resulted in a decreased survival rate of the newborn and potential for cataract formation in the survivors.

When pregnant rats and rabbits were treated with iv doses of dopamine there was **no** evidence of teratogenicity. However, the rabbit the drug showed embryocidal and fetotoxicity tendency.

Other than the previously reported nonclinical reproduction studies that are reported in the present label for dopamine, no new reports were retrieved in the literature search. Thus, no changes are recommended at this time for the label subsection on "**Pregnancy Category C.**" for proposed "**Pediatric use**" of dopamine injection.

No published reports were found indicating human developmental toxicity associated with dopamine treatment.

♦ **GENETIC TOXICOLOGY**: No studies were submitted by drug sponsor and none are required.

The present literature search revealed that **no** genotoxicity studies with dopamine.

Although for the Original **NDA 19-615** submission (Travenol Laboratories, **1986**), the drug sponsor had **not** conducted mutagenicity studies with dopamine, PHARMACOLOGY included at that time in the NDA Summary/Evaluation, the findings reported in two mutagenicity studies that were retrieved in the 1986 literature search (i.e., Suter et al in Mutation Research 137:17-18, 1984 and, Moldeus, P et al in Mutation Research 124:9-24, 1983). The drug sponsor agreed, at that time, to include the findings reported in these 2 studies in the label under the heading of "...Mutagenesis..." The findings in are still incorporated in the present day label for this the Baxter drug product- **Dopamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container, PL 2207**. Therefore, **no** further changes are needed, at this time, for the label under the heading "Mutagenesis."

"...Mutagenesis..." The findings in are still incorporated in the present day label for this the Baxter drug product- **Dopamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container, PL 2207**. Therefore, **no** further changes are needed, at this time, for the label under the heading "Mutagenesis."

♦ **LABELING:**

PHARMACOLOGY considers the language in the subsections under Precautions- "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy, Category C." adequate for **Dopamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container Viaflex** containing 0.8, 1.6 or 3.2 mg/ML of the active ingredient, and no changes are recommended, at this time.

Regarding **ADVERSE REACTIONS** observed in adult humans treated with iv infusions of dopamine (high doses of dopamine could cause elevation of BP via α-1-adrenergic receptors stimulation leading to vasoconstriction) and the recommended actions under **OVERDOSAGE** (i.e., the rate of dopamine infusion be reduced or temporarily discontinued until the patient's condition stabilizes and other measures may also instituted in the case that adult patient's fails to be stabilized), PHARMACOLOGY considers that changes, if any made, must be based on clinical experience with the pediatric population.

♦ **EVALUATION:**

The present NDA is a **Supplemental Application**, submitted by Baxter Healthcare Corporation in response to the FDA final rule - Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling **(59 FR 64240-64250; December 13, 1994)**.

Briefly, this final rule requires more complete information in a drug product's label about the use of the drug in the pediatric population (ages birth to 16 years). The final rule clearly applies to the present sponsor's prescription drug product Dopamine Hydrochloride and 5% Dextrose Injection, USP.

This final rule makes **no** specific requirements for new nonclinical studies for the use of Dopamine Hydrochloride and 5% Dextrose Injection, in a pediatric population. Thus, the presently approved portions of the label reporting nonclinical study findings (developmental toxicity and genotoxicity potential of dopamine) that are now applicable to the adult population, appear adequate at this time, for the pediatric population. (The developmental toxicity/genotoxicity data remain pertinent for the safe use of the drug in the adult population while the genotoxicity data are also pertinent to the pediatric population.)

Since no new nonclinical studies with dopamine hydrochloride were reported in this Supplemental Application and no new nonclinical studies are recommended that would further support the safe use of the drug in the pediatric population, no revisions are needed for the label subsections on "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy: Pregnancy Category C."

The final rule requires the labeling for a drug product containing one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, to note such risks in the "Contraindications," "Warnings," or "Precautions" section of the labeling. If toxicity data for the inactive ingredient(s) do not exit or are inconclusive, the label would not be required to contain a statement about an increased risk to the pediatric population. However, in such cases, FDA encourages drug applicants to collect and analyze data on inactive ingredients/preservatives that could represent a pediatric risk; these data may include those derived from human, animal or in vitro models studies (59 FR 64246-64247).

Drug sponsor asserts that this drug product does **not** contain any excipients that represent an increased risk of toxic effect in the pediatric population.

♦ **RECOMMENDATIONS:**

No new nonclinical studies with dopamine hydrochloride are required, at this time, to support the safe use of Dopamine Hydrochloride and 5% Dextrose Injection, USP in the proposed pediatric population. No changes are recommended for the language for the label subsections on **"Carcinogenesis, Mutagenesis, Impairment of Fertility"** and **"Pregnancy: Pregnancy Category C."**

If toxicity data for the inactive ingredient(s) used in this formulation do not exit or are inconclusive, FDA encourages the drug sponsor to collect and analyze data (human, animal and those derived from in vitro models) that could represent a pediatric risk, and note such risks in the **"Contraindications," "Warnings,"** or **"Precautions"** sections of the label.

cc
Orig NDA 19-615
HFD-110
HFD-110/RHPM
HFD-110/EAGBarry
HFD-345

/S/
9/1/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-615/S-012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB 23 2000 FROMM

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 19-615 (SE5-012) **SUBMISSION DATE:** June 22, 1999
Dopamine Hydrochloride and 5% Dextrose Injection,
USP in Plastic Container, PL 2207

Baxter Healthcare **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: PEDIATRIC LABELING SUPPLEMENT

BACKGROUND: Dopamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container is approved by the Agency for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure and chronic cardiac decompensation as in CHF. In compliance with the Final Rule {CFR 201.57(f)(9)(iii)} the sponsor provided a proposed labeling up-date for the use of Dopamine Hydrochloride and 5% Dextrose Injection in the pediatric population.

SYNOPSIS: In support of the proposed labeling up-date, the sponsor did a Medline search for the years 1966 to February 1997 and a search of the International Pharmaceutical Abstracts from 1970 to 1997. A total of 57 literature articles were identified, thirty articles were submitted four of which describe the pharmacokinetics (PK) of dopamine following infusion of Dopamine Injection to children age 2 days to 18 years. The four articles describing the PK of dopamine are summarized as follows:

Article #1: Allen, E, Pettigrew, A, Frank, D, Thompson, S, Myers, C, Yamashita, T and Blumer, JL, "Alterations in dopamine clearance and catechol-O-methyltransferace activity by dopamine infusions in children" Crit Care Med 1997; 25(1):181-9.

Summary: The clearance of dopamine and catechol-O-methyltransferace (COMT) activity levels were assessed in 14-dopamine treated and 5 untreated control patients aged 16 days to 12 years. There was age and concentration-dependent differences in clearance of dopamine that did not correlate with COMT activity. An ontogenetic profile was demonstrated in that younger patients (< 2 years) manifested a more rapid clearance of dopamine (more than 50% reduction per year) while in patients > 2 years dopamine clearance showed a much smaller age dependence, changing by about 50% during the next 10 years. Steady-state plasma dopamine concentration varied over almost a four-fold range among patients receiving the same nominal dose and a six-fold variation in dopamine clearance was observed. The factors that could contribute to this high variability include age, dopamine exposure (due to its non-linear PK, renal and hepatic impairment.

Article #12: Seri, I, Rudas, G, Bors, Z, Kanyicska, B, and Tulassay, T, "Effects of low-dose dopamine infusion on cardiovascular and renal functions, cerebral blood flow, and plasma catecholamine levels in sick preterm neonates" Pediatr Res 1993; 34(6):742-9.

Summary: Plasma catecholamine levels were measured in 61 preterm neonates (1-4 days old) following 2 and 4 μg/kg/min dopamine infusion and in 5 normotensive children (5-15 years old) following 2 μg/kg/min dopamine infusion of dopamine. Plasma dopamine clearance rates with 2 μg/kg/min dopamine infusion were significantly higher in children (100 ml/kg/min) than in preterm infants (40 ml/kg/min) resulting in more than double dopamine plasma levels in preterm neonates. In the preterm infants, plasma dopamine clearance was higher with 4 μg/kg/min (60 ml/kg/min) than with 2 μg/kg/min (40 ml/kg/min) of dopamine. The elevated steady-state plasma dopamine concentration in sick preterm neonates was said to be a consequence of their impaired metabolic function due to their early postnatal age and severe underlying disease.

Article #27: Notterman, DA, Greenwald, BM, Moran, F, DiMaio-Hunter, A, Metakis, L, Reidenberg, MM, "Dopamine clearance in critically ill infants and children: Effect of age and organ system dysfunction" Clin Pharmacol Ther 1990; 48(2):138-47.

Summary: To learn if there are age-related differences in the pharmacokinetic of dopamine, dopamine clearance was determined in 27 acutely ill children aged 2 days to 18 years who received continuous infusion of dopamine. There was a negative correlation between age and dopamine clearance with clearance being nearly twice as rapid in children younger than 2 years compared to older children (82.3 ± 27.7 ml/kg/min versus 45.93 ± 17.0 ml/kg/min). Clearance was lower in children with hepatic impairment (44.8 ± 28.6 ml/kg/min versus 70.1 ± 2.56 ml/kg/min for children with normal hepatic function based on measurement of conjugated bilurubin) and was lowest (29.8 ± 5.7 ml/kg/min) in four children with both hepatic and renal impairment.

Article #56: Zaritsky, A, Lotze, A, Stull, R, and Goldstein, D, "Steady-state dopamine clearance in critically ill infants and children" Crtit Care Med 1988; 16:217-20.

Summary: Steady-state pharmacokinetics of dopamine were examined in preterm and term infants as well as pediatric patients (total of 27 children) using dopamine infusion rate ranging from 0.57 μg/kg/min to 11 μg/kg/min. The variability in the clearances was very high. Dopamine clearance averaged 96.2 ± 55.4 ml/kg/min in 13 neonatal children (aged 1-47 days); 58.8 ± 51 ml/kg/min in 14 pediatric patients (aged 3 days to 15 years), and 25.1 ± 17.2 ml/kg/min in 6 patients with hepatic and renal dysfunction (resulting in more than 3-fold prolongation of dopamine clearances in these patients)

The draft revised labeling and marked-up copy of the current labeling are attached.

COMMENTS TO SENT TO THE SPONSOR:
The reports from the literature sited above emphasize the need to individually adjust the infusion rate of dopamine to obtain the desired hemodynamic effect of this drug and the need to use particular care when infusing dopamine into patients with renal or hepatic impairment. It is therefore recommended that the following statement should be added to the labeling:

Pediatric Use

Draft Labeling

RECOMMENDATION:
The Division of Pharmaceutical Evaluation I has reviewed the proposed labeling regarding the use of Dopamine Hydrochloride and 5% Dextrose Injection in the pediatric population and recommends that above statement be added to the labeling.

/S/ 2/23/2000

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by P Marroum, Ph.D. /S/ 2/23/2000

cc: NDA 19-615, HFD-110, HFD-860 (Fadiran, Mehta), BIOPHARM - CDR .

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-615/S-012

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PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

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NDA Number:	019615	**Trade Name:**	DOPAMINE HCL IN DEX INJ VIAFLEX PLASTIC
Supplement Number:	012	**Generic Name:**	DOPAMINE HYDROCHLORIDE
Supplement Type:	SE5	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	CORRECTION OF HEMODYNAMIC IMBALANCES PRESENT IN SHOCK DUE TO M I,TRAUMA,ENDOTOX-IC SEPTICEMIA,OPEN HEART SURGERY,RENAL FAILURE,& CHRONIC CARDIAC DECOMPENSATION
Action Date:	4/20/00		

Indication # 1 The correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic speticemia, open heart surgery, renal failure and chronic cardiac decompensation as in heart failure.

Label Adequacy: Adequate for ALL pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): S-012 submitted to provide additional pediatric labeling information pursuant to the Pediatric Rule

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	Adult	Completed	

This page was last edited on 4/5/01

/S/ 4/5/01

Signature Date