CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074815

Trade Name : ALPROSTADIL INJECTION USP

Generic Name: Alprostadil Injection USP 0.5mg/ml

Sponsor : Bedford Laboratories

Approval Date: January 20, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074815

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074815

APPROVAL LETTER

ANDA 74-815

JAN 20 1998

Bedford Laboratories
Attention: Robert V. Kasubick
300 Northfield Road
Bedford, OH 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated December 22, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Alprostadil Injection USP, 0.5 mg/mL.

Reference is also made to your amendment dated October 21, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Alprostadil Injection USP, 0.5 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Prostin VR Pediatric® 0.5 mg/mL of Pharmacia and Upjohn Co.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

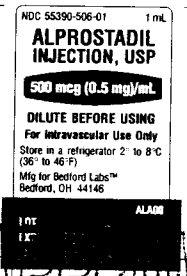
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074815

FINAL PRINTED LABELING

Note: Keyline does not print.

JAN 20 1998



APPROVED

Format: 42736 #082A
.8125" x 1.3125"
PMS 172 Orange, PMS Black

3 3/4

3 3/4

2 3/4

NDC 55390-506-01 5 x 1 mL ampules

ALPROSTADIL INJECTION, USP

500 mcg (0.5 mg) /mL

For Intravascular Use Only

BEDFORD LABORATORIES™

ALC00

LOT NO
EXP DATE

Usual Dosage: See package insert.

DILUTE BEFORE USING

Discard the infusion solution 24 hours after preparation.

Store in a refrigerator 2° to 8°C (36° to 46°F).

Each mL contains: Alprostadil, 500 mcg in dehydrated alcohol.

CAUTION - Federal law prohibits dispensing without prescription.

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

BEDFORD LABORATORIES™

Printed Side
Ben Venue
T082296D

Format Number: 282A
Black
172 Orange

BEDFORD LABORATORIES™

APPROVED

20 1998

ALPROSTADIL INJECTION, USP

WARNING

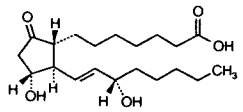
Apnea is experienced by about 10 to 12% of neonates with congenital heart defects treated with Alprostadil Injection, USP. Apnea is most often seen in neonates weighing less than 2 kg at birth and usually appears during the first hour of drug infusion. Therefore, respiratory status should be monitored throughout treatment, and Alprostadil Injection, USP should be used where ventilatory assistance is immediately available.

DESCRIPTION

Alprostadil Injection, USP for intravascular infusion contains 500 micrograms alprostadil, more commonly known as prostaglandin E_1, in 1 mL dehydrated alcohol.

The chemical name for alprostadil is (1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxy-1-octenyl]-5-oxocyclopentane heptanoic acid, and the molecular weight is 354.49.

Alprostadil is a white to off-white crystalline powder with a melting point between 110° and 116° C. Its solubility at 35° C is 8000 micrograms per 100 mL double distilled water. The structural formula is represented below:



Molecular Formula - $C_{20}H_{34}O_5$

CLINICAL PHARMACOLOGY

Alprostadil (prostaglandin E_1) is one of a family of naturally occurring acidic lipids with various pharmacologic effects. Vasodilation, inhibition of platelet aggregation, and stimulation of intestinal and uterine smooth muscle are among the most notable of these effects. Intravenous doses of 1 to 10 micrograms of alprostadil per kilogram of body weight lower the blood pressure in mammals by decreasing peripheral resistance. Reflex increases in cardiac output and rate accompany the reduction in blood pressure.

Smooth muscle of the ductus arteriosus is especially sensitive to alprostadil, and strips of lamb ductus markedly relax in the presence of the drug. In addition, administration of alprostadil reopened the closing ductus of new-born rats, rabbits, and lambs. These observations led to the investigation of alprostadil in infants who had congenital defects which restricted the pulmonary or systemic blood flow and who depended on a patent ductus arteriosus for adequate blood oxygenation and lower body perfusion.

In infants with restricted pulmonary blood flow, about 50% responded to alprostadil infusion with at least a 10 torr increase in blood pO_2 (mean increase about 14 torr and mean increase in oxygen saturation about 23%). In general, patients who responded best had low pretreatment blood pO_2 and were 4 days old or less.

In infants with restricted systemic blood flow, alprostadil often increased pH in those having acidosis, increased systemic blood pressure, and decreased the ratio of pulmonary artery pressure to aortic pressure.

Alprostadil must be infused continuously because it is very rapidly metabolized. As much as 80% of the circulating alprostadil may be metabolized in one pass through the lungs, primarily by β- and ω- oxidation. The metabolites are excreted primarily by the kidney, and excretion is essentially complete within 24 hours after administration. No unchanged alprostadil has been found in the urine, and there is no evidence of tissue retention of alprostadil or its metabolites.

INDICATIONS AND USAGE

Alprostadil injection is indicated for palliative, not definitive, therapy to temporarily maintain the patency of the ductus arteriosus until corrective or palliative surgery can be performed in neonates who have congenital heart defects and who depend upon the patent ductus for survival. Such congenital heart defects include pulmonary atresia, pulmonary stenosis, tricuspid atresia, tetralogy of Fallot, interruption of the aortic arch, coarctation of the aorta, or transposition of the great vessels with or without other defects.

In infants with restricted pulmonary blood flow, the increase in blood oxygenation is inversely proportional to pretreatment pO_2 values; that is, patients with low pO_2 values respond best, and patients with pO_2 values of 40 torr or more usually have little response.

Alprostadil injection should be administered only by trained personnel in facilities that provide pediatric intensive care.

CONTRAINDICATIONS

None.

WARNINGS

See **WARNING** box.

NOTE: Alprostadil injection must be diluted before it is administered. See dilution instructions in **DOSAGE AND ADMINISTRATION** section.

The administration of alprostadil injection to neonates may result in gastric outlet obstruction secondary to antral hyperplasia. This effect appears to be related to duration of therapy and cumulative dose of the drug. Neonates receiving alprostadil injection at recommended doses for more than 120 hours should be closely monitored for evidence of antral hyperplasia and gastric outlet obstruction.

Alprostadil injection should be infused for the shortest time and at the lowest dose that will produce the desired effects. The risks of long-term infusion of alprostadil injection should be weighed against the possible benefits that critically ill infants may derive from its administration.

PRECAUTIONS

General Precautions: Cortical proliferation of the long bones, first observed in dogs, has also been observed in infants during long-term infusions of alprostadil. The cortical proliferation in infants regressed after withdrawal of the drug.

In infants treated with alprostadil injection at the usual doses for 10 hours to 12 days and who died of causes unrelated to ductus structural weakness, tissue sections of the ductus and pulmonary arteries have shown intimal lacerations, a decrease in medial muscularity and disruption of the medial and internal elastic lamina. Localized and aneurysmal dilatations and vessel wall edema also were seen compared to a series of pathological specimens from infants not treated with alprostadil injection. The incidence of such structural alterations has not been defined.

Because alprostadil inhibits platelet aggregation, use alprostadil injection cautiously in neonates with bleeding tendencies.

Alprostadil injection should not be used in neonates with respiratory distress syndrome. A differential diagnosis should be made between respiratory distress syndrome (hyaline membrane disease) and cyanotic heart disease (restricted pulmonary blood flow). If full diagnostic facilities are not immediately available, cyanosis (pO_2 less than 40 torr) and restricted pulmonary blood flow apparent on an X-ray are appropriate indicators of congenital heart defects.

Necessary Monitoring: In all neonates, arterial pressure should be monitored intermittently by umbilical artery catheter, auscultation, or with a Doppler transducer. *Should arterial pressure fall significantly, decrease the rate of infusion immediately.*

In infants with restricted pulmonary blood flow, measure efficacy of alprostadil injection by monitoring improvement in blood oxygenation. In infants with restricted systemic blood flow, measure efficacy by monitoring improvement of systemic blood pressure and blood pH.

Drug Interactions: No drug interactions have been reported between alprostadil injection and the therapy standard in neonates with restricted pulmonary or systemic blood flow. Standard therapy includes antibiotics, such as penicillin and gentamicin; vasopressors, such as dopamine and isoproterenol; cardiac glycosides; and diuretics, such as furosemide.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term carcinogenicity studies and fertility studies have not been done. The Ames and Alkaline Elution assays reveal no potential for mutagenesis.

ADVERSE REACTIONS

Central Nervous System

Apnea has been reported in about 12% of the neonates treated. (See **WARNING** box.) Other common adverse reactions reported have been fever in about 14% of the patients treated and seizures in about 4%. The following reactions have been reported in less than 1% of the patients: cerebral bleeding, hyperextension of the neck, hyperirritability, hypothermia, jitteriness, lethargy, and stiffness.

Cardiovascular System

The most common adverse reactions reported have been flushing in about 10% of patients (more common after intraarterial dosing), bradycardia in about 7%, hypotension in about 4%, tachycardia in about 3%, cardiac arrest in about 1%, and edema in about 1%. The following reactions have been reported in less than 1% of the patients: congestive heart failure, hyperemia, second degree heart block, shock, spasm of the right ventricle infundibulum, supraventricular tachycardia, and ventricular fibrillation.

Respiratory System

The following reactions have been reported in less than 1% of the patients: bradypnea, bronchial wheezing, hypercapnia, respiratory depression, respiratory distress, and tachypnea.

Gastrointestinal System

See **WARNINGS**.

The most common adverse reaction reported has been diarrhea in about 2% of the patients. The following reactions have been reported in less than 1% of the patients: gastric regurgitation, and hyperbilirubinemia.

Hematologic System

The most common hematologic event reported has been disseminated intravascular coagulation in about 1% of the patients. The following events have been reported in less than 1% of the patients: anemia, bleeding, and thrombocytopenia.

Excretory System

Anuria and hematuria have been reported in less than 1% of the patients.

Skeletal System

Cortical proliferation of the long bones has been reported. See **PRECAUTIONS**.

Miscellaneous

Sepsis has been reported in about 2% of the patients. Peritonitis has been reported in less than 1% of the patients. Hypokalemia has been reported in about 1%, and hypoglycemia and hyperkalemia have been reported in less than 1% of the patients.

OVERDOSAGE

Apnea, bradycardia, pyrexia, hypotension, and flushing may be signs of drug overdosage. If apnea or bradycardia occurs, discontinue the infusion, and provide appropriate medical treatment. Caution should be used in restarting the infusion. If pyrexia or hypotension occurs, reduce the infusion rate until these symptoms subside. Flushing is usually a result of incorrect intraarterial catheter placement, and the catheter should be repositioned.

DOSAGE AND ADMINISTRATION

The preferred route of administration for alprostadil injection is continuous intravenous infusion into a large vein. Alternatively, alprostadil injection may be administered through an umbilical artery catheter placed at the ductal opening. Increases in blood pO_2 (torr) have been the same in neonates who received the drug by either route of administration.

Begin infusion with 0.05 to 0.1 micrograms alprostadil per kilogram of body weight per minute. A starting dose of 0.1 micrograms per kilogram of body weight per minute is the recommended starting dose based on clinical studies; however, adequate clinical response has been reported using a starting dose of 0.05 micrograms per kilogram of body weight per minute. After a therapeutic response is achieved (increased pO_2 in infants with restricted pulmonary blood flow or increased systemic blood pressure and blood pH in infants with restricted systemic blood flow), reduce the infusion rate to provide the lowest possible dosage that maintains the response. This may be accomplished by reducing the dosage from 0.1 to 0.05 to 0.025 to 0.01 micrograms per kilogram of body weight per minute. If response to 0.05 micrograms per kilogram of body weight per minute is inadequate, dosage can be increased up to 0.4 micrograms per kilogram of body weight per minute although, in general, higher infusion rates do not produce greater effects.

Dilution Instructions: To prepare infusion solutions, dilute 1 mL of Alprostadil Injection with Sodium Chloride Injection or Dextrose Injection. Undiluted Alprostadil Injection may interact with the plastic sidewalls of volumetric infusion chambers causing a change in the appearance of the chamber and creating a hazy solution. Should this occur, the solution and the volumetric infusion chamber should be replaced.

When using a volumetric infusion chamber, the appropriate amount of intravenous infusion solution should be added to the chamber first. The undiluted Alprostadil Injection solution should then be added to the intravenous infusion solution, avoiding direct contact of the undiluted solution with the walls of the volumetric infusion chamber.

Dilute to volumes appropriate for the pump delivery system available. Prepare fresh infusion solutions every 24 hours. *Discard any solution more than 24 hours old.*

Sample Dilutions and Infusion Rates to Provide a Dosage of 0.1 Micrograms per Kilogram of Body Weight per Minute

Add 1 ampule (500 mcg) alprostadil to:	Approximate Concentration of resulting solution (mcg/mL)	Infusion rate (mL/min/kg of body weight)
250 mL	2	0.05
100 mL	5	0.02
50 mL	10	0.01
25 mL	20	0.005

Example: To provide 0.1 micrograms/kilogram of body weight per minute to an infant weighing 2.8 kilograms using a solution of 1 ampule Alprostadil Injection, USP in 100 mL of saline or dextrose:

INFUSION RATE = 0.02 mL/min per kg x 2.8 kg = 0.056 mL/min or 3.36 mL/hr.

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

HOW SUPPLIED

Alprostadil Injection, USP is available in a carton of 5 x 1 mL ampules; **NDC 55390-506-01.**

Each mL contains 500 micrograms alprostadil in dehydrated alcohol.

Store in a refrigerator at 2° to 8° C (36° to 46° F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

August 1997

ALPI00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74815

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3

2. ANDA 74-815

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

4. LEGAL BASIS FOR SUBMISSION see next page

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Alprostadil Injection, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES: see next page

10. PHARMACOLOGICAL CATEGORY
Cardiovascular

11. Rx or OTC
Rx

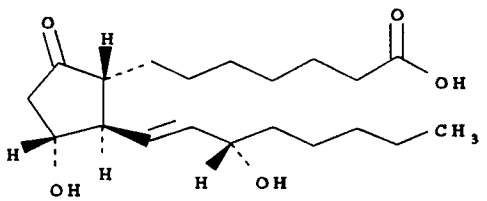
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM Injection

14. POTENCY 0.5 mg/mL

15. CHEMICAL NAME AND STRUCTURE
Alprostadil, USP

(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxy-1-octenyl]-5-oxo-cyclopentane heptanoic acid



$C_{20}H_{34}O_5$; M.W.=354.49 [*745-65-3*]

16. RECORDS AND REPORTS N/A

17. COMMENTS: N/A

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL

19. REVIEWER: J. L. Smith DATE COMPLETED: December 10, 1997

cc: ANDA 74-815
Division File
Field Copy

Endorsements:
HFD-623/J.Smith/12-10-97
HFD-623/V.Sayeed/12-12-97 12/15/97
X:\NEW\FIRMSAM\BEDFORD\LTRS&REV\74815AP3.CD
F/t by: bc/12-15-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074815

MICROBIOLOGY REVIEW(S)

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #2

June 30, 1997

A. 1. ANDA: **74-815**

APPLICANT: Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick
300 Northfield Road
Bedford, Ohio 44146

2. PRODUCT NAMES: **Alprostadil Injection**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

0.5 mg/mL sterile solution; 1 mL fill contained in a 2 cc glass ampule for intravascular injection only

4. METHOD(S) OF STERILIZATION:

5. PRINCIPLE INDICATIONS: For palliative, maintenance of ductus arteriosus patency in neonates

6. PHARMACOLOGICAL CATEGORY: Cardiovascular drug

B. 1. DATE OF INITIAL SUBMISSION: **December 22, 1995**

2. DATE OF AMENDMENT:

January 9, 1997 (Received by OGD on 1/10/97)
- Subject of this Review
Sent in response to the letter dated July 30, 1996

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: June 19, 1997

C. REMARKS: The information provided in the amendment was sufficient to determine that the applicant is taking the necessary steps to ensure the sterility of the subject drug product (Alprostadil Injection).

D. CONCLUSIONS: The submissions are therefore now recommended for approval on the basis of sterility assurance.

6/30/97
Kenneth H. Muhvich, Ph.D.

HFD-620/initialed by RPatel
drafted by: KHMuhvich, 6/30/97

cc:

Original ANDA **74-815**
Field Copy

6/30/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074815

BIOEQUIVALENCE REVIEW(S)

APR 10 1996

Alprostadil Injection, USP
0.5 mg/ml, 1 ml ampule
ANDA #74-815
Reviewer: A. P. Patel
File: x\apatel\74815w.d95

Bedford Laboratories™
Bedford, Ohio
Submission Date:
Dec. 22, 1995

Review of a Waiver Request

Objective:

The firm is requesting a waiver of *in vivo* bioequivalence study requirements for its Alprostadil Injection, USP, 0.5 mg/ml; 1 ml per vial, based on 21 CFR 320.22 (b)(1). The approved reference product Prostin VR Pediatric® Injection (0.5 mg/ml alprostadil for injection, USP) manufactured by Upjohn Co. The product is intended for intravascular use only.

Introduction:

Alprostadil is used to temporarily maintain the patency of the ductus arterious until corrective or palliative surgery can be performed in neonates who have congenital heart defects and who depend upon the patent ductus for survival.

Comment:

i **Comparative formulation:** Please Table 1.

ii As shown in Table 1, the proposed test product contains the same active and inactive ingredients in the same quantities per vial as the approved reference product.

iii A waiver for *in vivo* bioequivalent study can be granted pursuant to Title 21 CFR §320.22 (b)(1) of Bioavailability/Bioequivalence Regulations.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories™, demonstrates that Alprostadil Injection, USP 0.5 mg/ml; 1 ml/vial falls under Title 21 CFR 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. Waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation manufactured by Bedford Laboratories™, to be bioequivalent to Prostin VR Pediatric® Injection (0.5 mg/ml alprostadil for injection, USP) manufactured by Upjohn Co.

The firm should be informed of the above recommendation.

4/9/96

A.P.Patel