CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

10-515/S023

Trade Name: Isuprel®

Generic Name: isoproterenol hydrochloride

Sponsor: Hospira, Inc.

Approval Date: 2/23/2000

Indication: Isoproterenol hydrochloride injection is indicated:
• For mild or transient episodes of heart block that do not require electric shock or pacemaker therapy.
• For serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia or fibrillation).
• For use in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, is available.
• For bronchospasm occurring during anesthesia.
• As an adjunct to fluid and electrolyte replacement therapy and the use of other drugs and procedures in the treatment of hypovolemic and septic shock, low cardiac output (hypoperfusion) states, congestive heart failure, and cardiogenic shock.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S023

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S023

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 23 2000

NDA 10-515/S-023

Abbott Laboratories
Attention: Ms. Leslie Koehler
200 Abbott Park Road
D-389, Bldg. AP30
Abbott Park, Illinois 60064-6157

Dear Ms. Koehler:

Please refer to your supplemental new drug application dated September 11, 1998, received September 16, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isuprel (isoproterenol hydrochloride) Injection.

We acknowledge receipt of your submission dated November 12, 1999 that constituted a complete response to our September 29, 1999 action letter.

This supplemental new drug application provides for final printed labeling revised to create under **PRECAUTIONS**, a new **Geriatric Use** subsection that reads as follows:

> Clinical studies of Isuprel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects in clinical circumstances. There are, however, some data that suggest that elderly healthy or hypertensive patients are less responsive to beta-adrenergic stimulation than are younger subjects. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

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 dated November 12, 1999). 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 Project Manager
(301) 594-5313

Sincerely,

RJ 2/23/00

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

cc:
Archival NDA 10-515
HFD-110/Div. Files
HFD-110/E.Fromm
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

E. Fromm 2/23/00

Drafted by: ef/November 24, 1999
Initialed by: K Jongedyk/2/2/00
K Srinivasachar/2/4/00
E Fadiran/2/4/00
P Marroum/2/4/00
C Resnick/2/4/00
S Chen/2/4/00
N Morgenstern/2/15/00
Final: asb/2/17/00
Filename: 10-515(ap).doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S023

LABELING

Labeling: ORIGINAL
NDA No: 10-515 Rec'd. 11-17-99
Reviewed by: [signature] 2/23/00

RA06151-R1-Rev. Oct., 1999

3 2000

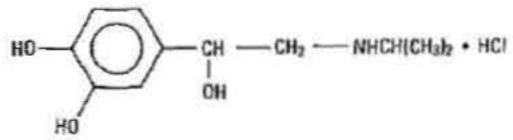
ISUPREL®

Isoproterenol Hydrochloride Injection, USP

Sterile Injection 1:5000

DESCRIPTION

Isoproterenol hydrochloride is 3,4-Dihydroxy-α-[(isopropylamino)methyl] benzyl alcohol hydrochloride, a synthetic sympathomimetic amine that is structurally related to epinephrine but acts almost exclusively on beta receptors. The molecular formula is $C_{11}H_{17}NO_3 \cdot HCl$. It has a molecular weight of 247.72 and the following structural formula:



Isoproterenol hydrochloride is a racemic compound.

Each milliliter of the sterile 1:5000 solution contains:		
ISUPREL, brand of isoproterenol hydrochloride injection, USP		0.2 mg
Lactic Acid		0.12 mg
Sodium Chloride		7.0 mg
Sodium Lactate		1.8 mg
Sodium Metabisulfite		1.0 mg
Water for Injection	qs ad	1.0 mL

The pH is adjusted between 2.5 and 4.5 with hydrochloric acid.

The sterile 1:5000 solution is nonpyrogenic and can be administered by the intravenous, intramuscular, subcutaneous, or intracardiac routes.

CLINICAL PHARMACOLOGY

Isoproterenol is a potent nonselective beta-adrenergic agonist with very low affinity for alpha-adrenergic receptors. Intravenous infusion of isoproterenol in man lowers peripheral vascular resistance, primarily in skeletal muscle but also in renal and mesenteric vascular beds. Diastolic pressure falls. Renal blood flow is decreased in normotensive subjects but is increased markedly in shock. Systolic blood pressure may remain unchanged or rise, although mean arterial pressure typically falls. Cardiac output is increased because of the positive inotropic and chronotropic effects of the drug in the face of diminished peripheral vascular resistance. The cardiac effects of isoproterenol may lead to palpitations, sinus tachycardia, and more serious arrhythmias; large doses of isoproterenol may cause myocardial necrosis in animals.

Isoproterenol relaxes almost all varieties of smooth muscle when the tone is high, but this action is most pronounced on bronchial and gastrointestinal smooth muscle. It prevents or relieves bronchoconstriction, but tolerance to this effect develops with overuse of the drug.

In man, isoproterenol causes less hyperglycemia than does epinephrine. Isoproterenol and epinephrine are equally effective in stimulating the release of free fatty acids and energy production.

Absorption, Fate, and Excretion. Isoproterenol is readily absorbed when given parenterally or as an aerosol. It is metabolized primarily in the liver and other tissues by COMT. Isoproterenol is a relatively poor substrate for MAO and is not taken up by sympathetic neurons to the same extent as are epinephrine and norepinephrine. The duration of action of isoproterenol may therefore be longer than that of epinephrine, but is still brief.

INDICATIONS AND USAGE

Isoproterenol hydrochloride injection is indicated:

- For mild or transient episodes of heart block that do not require electric shock or pacemaker therapy.
- For serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia or fibrillation). (See CONTRAINDICATIONS.)
- For use in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, is available. (See CONTRAINDICATIONS.)
- For bronchospasm occurring during anesthesia.
- As an adjunct to fluid and electrolyte replacement therapy and the use of other drugs and procedures in the treatment of hypovolemic and septic shock, low cardiac output (hypoperfusion) states, congestive heart failure, and cardiogenic shock. (See WARNINGS.)

CONTRAINDICATIONS

Use of isoproterenol hydrochloride injection is contraindicated in patients with tachyarrhythmias; tachycardia or heart block caused by digitalis intoxication; ventricular arrhythmias which require inotropic therapy; and angina pectoris.

WARNINGS

Isoproterenol hydrochloride injection, by increasing myocardial oxygen requirements while decreasing effective coronary perfusion, may have a deleterious effect on the injured or failing heart. Most experts discourage its use as the initial agent in treating cardiogenic shock following myocardial infarction. However, when a low arterial pressure has been elevated by other means, isoproterenol hydrochloride injection may produce beneficial hemodynamic and metabolic effects.

In a few patients, presumably with organic disease of the AV node and its branches, isoproterenol hydrochloride injection has paradoxically been reported to worsen heart block or to precipitate Adams-Stokes attacks during normal sinus rhythm or transient heart block.

Contains sodium metabisulfite, 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.

PRECAUTIONS

General

Isoproterenol hydrochloride injection should generally be started at the lowest recommended dose. This may be gradually increased if necessary while carefully monitoring the patient. Doses sufficient to increase the heart rate to more than 130 beats per minute may increase the likelihood of inducing ventricular arrhythmias. Such increases in heart rate will also tend to increase cardiac work and oxygen requirements which may adversely affect the failing heart or the heart with a significant degree of arteriosclerosis.

Particular caution is necessary in administering isoproterenol hydrochloride injection to patients with coronary artery disease, coronary insufficiency, diabetes, hyperthyroidism, and sensitivity to sympathomimetic amines.

Adequate filling of the intravascular compartment by suitable volume expanders is of primary importance in most cases of shock and should precede the administration of vasoactive drugs. In patients with normal cardiac function, determination of central venous pressure is a reliable guide during volume replacement. If evidence of hypoperfusion persists after adequate volume replacement, isoproterenol hydrochloride injection may be given.

In addition to the routine monitoring of systemic blood pressure, heart rate, urine flow, and the electrocardiograph, the response to therapy should also be monitored by frequent determination of the central venous pressure and blood gases. Patients in shock should be closely observed during isoproterenol hydrochloride injection administration. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease the infusion rate or temporarily discontinue the infusion. Determinations of cardiac output and circulation time may also be helpful. Appropriate measures should be taken to ensure adequate ventilation. Careful attention should be paid to acid-base balance and to the correction of electrolyte disturbances. In cases of shock associated with bacteremia, suitable antimicrobial therapy is, of course, imperative.

Drug Interactions

Isoproterenol hydrochloride injection and epinephrine should not be administered simultaneously because both drugs are direct cardiac stimulants and their combined

effects may induce serious arrhythmias. The drugs may, however, be administered alternately provided a proper interval has elapsed between doses.

ISUPREL should be used with caution, if at all, when potent inhalational anesthetics such as halothane are employed because of potential to sensitize the myocardium to effects of sympathomimetic amines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of isoproterenol hydrochloride have not been done. Mutagenic potential and effect on fertility have not been determined. There is no evidence from human experience that isoproterenol hydrochloride injection may be carcinogenic or mutagenic or that it impairs fertility.

Pregnancy Category C

Animal reproduction studies have not been conducted with isoproterenol hydrochloride. It is also not known whether isoproterenol hydrochloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Isoproterenol hydrochloride should be given to a pregnant woman only if clearly needed.

Nursing Mothers

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

Pediatric Use

Safety and efficacy of isoproterenol in pediatric patients have not been established.

Intravenous infusions of isoproterenol in refractory asthmatic children at rates of 0.05-2.7 µg/kg/min have caused clinical deterioration, myocardial necrosis, congestive heart failure and death. The risks of cardiac toxicity appear to be increased by some factors (acidosis, hypoxemia, coadministration of corticosteroids, coadministration of methylxanthines (theophylline, theobromine) or aminophylline) that are especially likely to be present in these patients. If I.V. isoproterenol is used in children with refractory asthma, patient monitoring must include continuous assessment of vital signs, frequent electrocardiography, and daily measurements of cardiac enzymes, including CPK-MB.

Geriatric Use

Clinical studies of Isuprel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects in clinical circumstances. There are, however, some data that suggest that elderly healthy or hypertensive patients are less responsive to beta-adrenergic stimulation than are younger subjects. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

ADVERSE REACTIONS

The following reactions to isoproterenol hydrochloride injection have been reported:

CNS: Nervousness, headache, dizziness, nausea, visual blurring.

Cardiovascular: Tachycardia, palpitations, angina, Adams-Stokes attacks, pulmonary edema, hypertension, hypotension, ventricular arrhythmias, tachyarrhythmias.

In a few patients, presumably with organic disease of the AV node and its branches, isoproterenol hydrochloride injection has been reported to precipitate Adams-Stokes seizures during normal sinus rhythm or transient heart block.

Respiratory: Dyspnea.

Other: Flushing of the skin, sweating, mild tremors, weakness, pallor.

OVERDOSAGE

The acute toxicity of isoproterenol hydrochloride in animals is much less than that of epinephrine. Excessive doses in animals or man can cause a striking drop in blood pressure, and repeated large doses in animals may result in cardiac enlargement and focal myocarditis.

In case of accidental overdosage as evidenced mainly by tachycardia or other arrhythmias, palpitations, angina, hypotension, or hypertension, reduce rate of administration or discontinue isoproterenol hydrochloride injection until patient's condition stabilizes. Blood pressure, pulse, respiration, and EKG should be monitored.

It is not known whether isoproterenol hydrochloride is dialyzable.

The oral LD_{50} of isoproterenol hydrochloride in mice is 3,850 mg/kg ± 1,190 mg/kg of pure drug in solution.

DOSAGE AND ADMINISTRATION

ISUPREL injection 1:5000 should generally be started at the lowest recommended dose and the rate of administration gradually increased if necessary while carefully

monitoring the patient. The usual route of administration is by intravenous infusion or bolus intravenous injection. In dire emergencies, the drug may be administered by intracardiac injection. If time is not of the utmost importance, initial therapy by intramuscular or subcutaneous injection is preferred.

Recommended dosage for adults with heart block, Adams-Stokes attacks, and cardiac arrest:

Route of Administration	Preparation of Dilution	Initial Dose	Subsequent Dose Range*
Bolus intravenous injection	Dilute 1 mL (0.2 mg) to 10 mL with Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP	0.02 mg to 0.06 mg (1 mL to 3 mL of diluted solution)	0.01 mg to 0.2 mg (0.5 mL to 10 mL of diluted solution)
Intravenous infusion	Dilute 10 mL (2 mg) in 500 mL of 5% Dextrose Injection, USP	5 mcg/min. (1.25 mL of diluted solution per minute)	
Intramuscular	Use Solution 1:5000 undiluted	0.2 mg (1 mL)	0.02 mg to 1 mg (0.1 mL to 5 mL)
Subcutaneous	Use Solution 1:5000 undiluted	0.2 mg (1 mL)	0.15 mg to 0.2 mg (0.75 mL to 1 mL)
Intracardiac	Use Solution 1:5000 undiluted	0.02 mg (0.1 mL)	

*Subsequent dosage and method of administration depend on the ventricular rate and the rapidity with which the cardiac pacemaker can take over when the drug is gradually withdrawn.

There are no well-controlled studies in children to establish appropriate dosing; however, the American Heart Association recommends an initial infusion rate of 0.1 mcg/kg/min, with the usual range being 0.1 mcg/kg/min to 1 mcg/kg/min.

Recommended dosage for adults with shock and hypoperfusion states:

Route of Administration	Preparation of Dilution†	Infusion Rate††
Intravenous infusion	Dilute 5 mL (1 mg) in 500 mL of 5% Dextrose Injection, USP	0.5 mcg to 5 mcg per minute (0.25 mL to 2.5 mL of diluted solution)

† Concentrations up to 10 times greater have been used when limitation of volume is essential.

†† Rates over 30 mcg per minute have been used in advanced stages of shock. The rate of infusion should be adjusted on the basis of heart rate, central venous pressure, systemic blood pressure, and urine flow. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease or temporarily discontinue the infusion.

Recommended dosage for adults with bronchospasm occurring during anesthesia:

Route of Administration	Preparation of Dilution	Initial Dose	Subsequent Dose
Bolus intravenous injection	Dilute 1 mL (0.2 mg) to 10 mL with Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP	0.01 mg to 0.02 mg (0.5 mL to 1 mL of diluted solution)	The initial dose may be repeated when necessary

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Such solution should not be used.

HOW SUPPLIED

List	Container	Concentration	Fill	Quantity
1410	Ampul	0.2 mg (0.2 mg/mL)	1 mL	UNI-AMP® pak of 25
1410	Ampul	1 mg (0.2 mg/mL)	5 mL	10 ampuls per carton

Protect from light. Keep in opaque container until used.
Store in a cool place between 8° to 15°C (46° to 59°F).

Do not use if the injection is pinkish or darker than slightly yellow or contains a precipitate.

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S023

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB - 1 2000

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 10-515 (SLR-023) **SUBMISSION DATE:** November 12, 1999
Isuprel® (Isopreterenol Hydrochloride) Injection,
USP Sterile Injection 1:5000

Abbot Laboratories **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: GERIATRIC LABELING SUPPLEMENT

BACKGROUND: Isuprel® (Isopreterenol Hydrochloride) Injection is a non-selective beta-adrenergic agonist with very low affinity for alpha-adrenagic receptors approved by the Agency for the treatment of heart block and cardiac arrest. In compliance with the Final Rule {CFR 201.57(f)(10)(iv)} the sponsor provided a proposed text to be added to Isuprel injection labeling in the **Precautions**/Geriatric Use subsection and this was reviewed and comments were sent to the sponsor on September 29, 1999.

SYNOPSIS: The sponsor has incorporated the changes requested by the Agency into the labeling for Isuprel injection with respect to geriatric use (See attached proposed and final printed labeling).

RECOMMENDATION:
The Division of Pharmaceutical Evaluation I has reviewed the proposed labeling regarding the use of Isuprel injection in the geriatric population and finds that the sponsor has incorporated the changes requested by the Agency. No further action is needed at this time.

2/1/2000

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

FT Initialed by P Marroum, Ph.D. 2/1/2000

cc: NDA 10-515, HFD-110, HFD-860 (Fadiran, Mehta), BIOPHARM - CDR .

5 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S023

OTHER REVIEW(S)

FEB 23 2000

CSO Review of Final Printed Labeling

Application: NDA 10-515/S-023
Isuprel (isoproterenol hydrochloride) Injection

Applicant: Abbott Laboratories

Document Date: November 12, 1999

Receipt Date: November 17, 1999

Type of Supplement: Geriatric Labeling Supplement

Background: This supplement was submitted in accordance with 21 CFR 201.57(f)(10) and provides for final printed labeling (FPL) revised under **PRECAUTIONS** to create a new **Geriatric Use** subsection.

An approvable letter was issued September 29, 1999.

The sponsor submitted final printed labeling in a submission dated November 12, 1999. The **PRECAUTIONS: Geriatric Use** subsection was revised as follows:

> Clinical studies of Isuprel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects in clinical circumstances. There are, however, some data that suggest that elderly healthy or hypertensive patients are less responsive to beta-adrenergic stimulation than are younger subjects. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

Comments/Recommendations: The changes in the labeling supplement (S-023) were made in accordance with the instructions in the approvable letter dated September 29, 1999. An approval letter will be drafted for Dr. Lipicky's signature.

Edward Fromm
Consumer Safety Officer

Ef/2-15-00

cc: NDA 10-515
HFD-2
HFD-110
HFD-110/EFromm
HFD-110/Blount