DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 10-515/S-022

MAY 4 1999

Abbott Laboratories
Attention: Ms. Jean Conaway
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Conaway:

Please refer to your supplemental new drug application dated December 31, 1997, received January 5, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isuprel (isoproterenol hydrochloride) Injection.

We acknowledge receipt of your submissions dated February 5 and April 9, 1999. Your submission of April 9, 1999 constituted a complete response to our September 15, 1998 action letter.

This supplemental new drug application provides for final printed labeling revised as required in the December 13, 1994 Federal Register notice relating to the revision of the "Pediatric Use" subsection of the labeling.

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 final printed labeling included in your April 9, 1999 submission. 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. Gary Buehler
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,

/S/

5/4/99

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 10515/S022

FINAL PRINTED LABELING

APPROVED
MAY 4 1999

58-0649 -R4-Rev. Feb., 1999

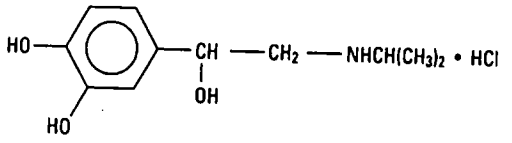
ISUPREL®

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 (as preservative)	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 air in the ampuls has been displaced by nitrogen gas.

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.

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.

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ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 10515/S022

MEDICAL REVIEW(S)

DF

JAN 23 1998

MEDICAL OFFICER REVIEW

NDA #:	[redacted]	Document ID #:	SLR-022
DRUG NAME:	Isuprel® Sterile Injection 1:5000 (Isoproterenol HCl injection, USP)		
SPONSOR:	Abbott Hospital Products Division		
TYPE OF DOCUMENT:	Pediatric Supplement - Amendment		
DATE OF CORRESPONDENCE:	*31-Dec-1997*	*DATE ASSIGNED:*	*22-Jan-1998*
DATE RECEIVED:	*05-Jan-1998*	*DATE COMPLETED*	*23-Jan-1998*
MEDICAL OFFICER:	Khin Maung U, M.D.		

PHARMACOLOGY

Generic: Isoproterenol HCL injection, USP, sterile injection 1:5000 & 1:50,000

Chemical: 3,4-Dihydroxy-alpha-[(isopropylamino)methyl] benzyl alcohol hydrochloride. It is a synthetic sympathomimetic amine that is structurally related to epinephrine but acts almost exclusively on beta receptors.

SUBMISSION:

Abbott Laboratories submitted an application for the following changes in package insert labeling related to "**pediatric use**" for Isuprel®:-

(i) Indications and Usage: The sponsor proposed to add a new indication:

(ii) Warnings: The sponsor proposed to insert the following paragraph under this section.

(iii) Precautions: The sponsor proposed the following paragraph related to Drug Interactions to be inserted under this section of Labeling.

(iv) Pediatric Use: The sponsor proposed to insert a paragraph on Pediatric Use as follows:

(v) Adverse Reactions: The sponsor proposed addition of the following under Adverse Reactions:

- *"CNS: Nausea, visual blurring*
- *Respiratory: Dyspnea*
- *Other: Pallor"*

(vi) Overdosage: The sponsor proposed to insert the following paragraph under this section:

(vii) Dosage and Administration: The sponsor proposed to insert the following three items under this section:

REVIEW

This review is limited to the pediatric supplement - amendment submitted together with the background literature provided. In addition, a literature search revealed more recent scientific publications pertinent to this submission which also are reviewed to obtain an objective opinion based on available information related to the proposed labeling changes. As there are seven sections in which labeling changes are proposed in the submission (rather than labeling changes confined to the "Pediatric Use Subsection in the Labeling" as alleged in the submission letter), the relevant scientific literature is reviewed within the context of each of the proposed labeling changes.

REVIEW OF SCIENTIFIC INFORMATION RELATED TO PROPOSED LABELING CHANGES AND THE REVIEWER'S RECOMMENDATIONS

I **Proposed labeling change related to Indications and Usage:**

The sponsor proposed addition of a new indication for Isoproterenol:

Isuprel is a potent bronchodilator making it useful in status asthmaticus. The sponsor submitted 1 article related to the indication for use of isoproterenol in the treatment of . Four recent publications relevant to this subject were found in literature search[2-5]. A brief review of each article is given in Appendix 1.

Rationale: When steroids, inhaled ß-2 agonists and maximum levels of aminophylline fail to reverse respiratory failure, intravenous isoproterenol infusion has been advocated to avoid the need for endotracheal intubation and mechanical ventilation (and its complications such as barotrauma and decreased mobilization of tenacious bronchial secretions). Intravenous isoproterenol infusion in life-threatening childhood status asthmaticus is reported to be an effective treatment[1,4,5]. However, no controlled studies of intravenous isoproterenol compared to another drug or placebo have been reported in the setting of ' . Complications of intravenous isoproterenol infusion include tachycardia, decreased splanchnic and renal blood flow, increased myocardial oxygen consumption and systemic arteriolar dilatation. Oxygen should always be administered during isoproterenol infusions in patients with asthma, and ECG and arterial blood gases must be carefully monitored. In the presence of acidosis or coexistent cardiac disease, isoproterenol may induce arrhythmias. Thus, the risks of complications from intravenous isoproterenol may outweigh its usefulness, especially since other more selective ß-2 agonists for intravenous use such as salbutamol[6] and terbutaline are now available and are more effective than aminophylline in producing bronchodilation with less side effects on heart rate than intravenous Isuprel.

Recommendation: While there is a few uncontrolled, non-double-blind data related to usefulness of intravenous isoproterenol infusion in severe life-threatening childhood status asthmaticus unresponsive to standard initial medical therapy, the studies were too few, there is insufficient information {CFR §314.125(b)(4)} about the drug to determine whether the drug is safe for use under the conditions recommended, and there is a lack of substantial evidence consisting of adequate and well-controlled double-blind clinical trials {CFR §314.125(b)(5) and CFR §314.126} of adequate sample size and statistical power to enable evaluation of safety and efficacy of intravenous isoproterenol for this indication. Thus, the submission for an indication to use Isuprel injection intravenously *for treatment of*:

NOT approvable.

I I **Proposed labeling change related to Warnings:**

The sponsor proposed insertion of the following paragraph under this section:

Isuprel can cause cardiotoxic effects through myocardial ischemia, particularly in patients with severe asthma who are hypoxic. The sponsor submitted 3 articles[7-9] and 2 more articles[10,11] were found related to the cardiotoxic effects of isoproterenol to be considered for the above paragraph that is proposed for insertion in the Warnings section of the label. A brief review of each article is given in Appendix 2.

Rationale: Myocardial ischemia is the proposed mechanism of isoproterenol-mediated cardiotoxicity. Isoproterenol increases the oxygen demand of the myocardium and causes peripheral vasodilatation. Differential myocardial vasodilatation in which isoproterenol causes inappropriately increased flow through healthier vessels thus shunting blood away from less responsive diseased vessels described as isoproterenol coronary steal syndrome, has been reported[10]. In the five articles reviewed[7-11], evidence for myocardial ischemia was demonstrated by elevation of CPK-MB enzymes and ECG changes in patients treated for severe asthma with intravenous isoproterenol infusion. Two instances[7-8] were associated with cardiac arrest and death; postmortem examination in one revealed multiple areas of myocardial necrosis[8]. These ischemic cardiotoxic effects of intravenous isoproterenol infusion may lead to complications including tachycardia, and, in the presence of acidosis or coexistent cardiac disease, intravenous isoproterenol infusion may induce arrhythmias. Thus, oxygen should always be administered during isoproterenol infusions in patients with asthma, and ECG, serum cardiac enzymes and arterial blood gases must be carefully monitored.

Recommendation: This part of the submission for an insertion of the proposed paragraph in the Warnings section is misleading {CFR §314.125(b)(6)} in that there is no mention of the potentially fatal myocardial necrosis which, for safety reasons, should be mentioned up front. Thus, this part of the submission is **NOT approvable.**

[If the sponsor incorporates more accurate (and annotated) information, a paragraph may be inserted, for example, as follows:

III **Proposed labeling change related to Precautions:**

The sponsor proposed inserting the following paragraph related to Drug Interactions under this section of Labeling:

As mentioned in the previous section, isoproterenol can cause cardiotoxic effects through myocardial ischemia, particularly in patients with severe asthma who are hypoxic. The sponsor submitted 2 articles[8,13] and literature search provided 3 other articles[9-11] related to the subject of interaction between intravenous isoproterenol and intravenous aminophylline or/and intravenous corticosteroids as background literature to be considered for evaluating whether the above paragraph may be inserted in the Precautions section of the label. A brief review of each article is given in Appendix 2.

Rationale: As discussed in the previous section, intravenous isoproterenol is cardiotoxic and may cause fatal myocardial necrosis[8]. This cardiac toxicity is enhanced by the concomitant use of intravenous methyl xanthines (aminophylline, theophylline)[8-11,13] and intravenous corticosteroids[8-11] which are often administered to patients with severe asthma. The importance of cardiac and blood gas monitoring is emphasized.

Recommendation: For this part of the submission for an insertion of the proposed paragraph in the Precautions section, there is insufficient information {CFR §314.125(b)(4)} about the drug to determine whether the drug is safe for use under the conditions recommended.

Thus, this part of the submission is **NOT approvable**. If the sponsor incorporates more accurate (and annotated) information, a paragraph may be inserted, for example, as follows:

IV **Proposed labeling change related to Pediatric Use:**

The sponsor proposed inserting a paragraph on Pediatric Use as follows:

The sponsor submitted "Medical Rationale" that revision of labeling is justified *"because of sufficient documentation in the literature that support the addition of data to the package insert"*. However, the sponsor provided no references in support of the proposed change related to Pediatric Use.

The sponsor also submitted that the *"pharmacological effects of Isoproterenol hydrochloride seen in adults is similar to that seen in pediatric patients. Likewise adverse experiences are similar and caution should be noted with its use in all patients*[i,ii,iii]*"*.

i. The Harriet Lane Handbook, 13th edition, Johnson K (ed.), Mosby 1993
ii. The Pediatric Drug Handbook, 3rd Edition, Benitz WE, Tatro DS (eds.). Mosby, 1995.
iii. Maguire JF, O'Rouke P, Colan SD, et al. Cardiotoxicity during treatment of severe childhood asthma. Pediatrics 1991; 88(6): 1180-86.

The sponsor also mentioned that *"Data will be submitted for all age categories (neonates to adolescents) with the exception of neonates, infants and children for the indication of unexplained syncope. There is no available documentation to support this indication in those age groups"*. However, there was no *"data"* submitted by the sponsor.

To review the scientific basis for this proposed pediatric labeling change, a literature search and review of published articles on the pharmacokinetics and clinical use of intravenous isoproterenol infusion in pediatric populations[14-16] (which were rather scarce) were made. A brief review of each article is given in Appendix 3.

Rationale: At present, the information available from published studies on pharmacokinetics, safety and clinical use of intravenous isoproterenol infusion in children is not yet adequate to establish definitive indications and therapeutic guidelines which should be "based on substantial evidence derived from adequate and well-controlled studies in children". Catecholamine therapy based on studies in adults is not necessarily applicable to the child or infant, because of differences in cardiovascular and adrenergic physiology[14]. Animal studies suggest that pediatric patients are less responsive to exogenous catecholamines than are adults (e.g., the peripheral vascular effects of isoproterenol in young animals are also less than those in adults and increase with age)[14]. Also, the etiology, nature and course of diseases in children are not sufficiently similar to those in adults and therefore would not permit extrapolation from adult data to children.

ß-adrenergic receptors of neonates respond differently than adults to changes in blood pressure resulting from sepsis, hypoxia, hypovolemia, etc. The response of beta adrenergic receptors to catecholamines is different in small neonates, young children and adults. This may lead to differences in pharmacokinetics and clinical response.

Pharmacokinetics of intravenous isoproterenol infusion in critically ill infants have been studied in two disparate groups (postoperative cardiac patients and reactive airway disease) of relatively small numbers (total = 19) of children[15]. Postoperative cardiac patients received significantly lower dosing rate, their plasma concentrations of isoproterenol were lower, and the clearance of isoproterenol lower than reactive airway disease patients. Pharmacokinetic and pharmacodynamic studies for different age categories of pediatric population

(birth up to one month (neonates), 1 month up to 2 years (infants), 2 years up to 12 years (children) and 12 years up to 16 years (adolescents), etc.) require to be carried out and the doses to be used in different pediatric settings (e.g., status asthmaticus, bradycardia) need to be established.

The clinical conditions in which isoproterenol is used in pediatric settings (status asthmaticus or refractory asthma and bradycardia), the differences in the pharmacokinetics of intravenous isoproterenol infusion and the variability in clinical response because of the differences in ß-receptors in various organs in relation to age (gestational and chronological), hepatic and renal function, and adverse effects observed in pediatric settings (such as myocardial ischemia) suggest that these are not sufficiently similar to adults and would not therefore permit the extrapolation of adult data to be used in children.

Recommendation: Based on the above considerations and relevant information from the references[1-16] in Appendix 1 to Appendix 5, there is a lack of substantial evidence in pediatric patients consisting of well-controlled, double-blind clinical trials in the pediatric population {CFR §314.125(b)(5) and CFR §314.126} of adequate sample size and statistical power. Thus, this part of the application for insertion of a paragraph related to Pediatric Use in the package insert is recommended **NOT approvable.**

It is recommended that the information from current literature be made available in the package insert to enable physicians and pediatricians to make informed decisions regarding use of intravenous isoproterenol infusion in pediatric settings.

V **Proposed labeling change related to Adverse Reactions:**

The sponsor proposed adding the following under Adverse Reactions:

- *"CNS: Nausea, visual blurring*
- *Respiratory: Dyspnea*
- *Other: Pallor"*

Isoproterenol has cardiovascular and nervous system effects which may lead to the symptoms described in the proposed addition to the insert. Thus, this part of the submission for an insertion of the proposed paragraph in the Adverse Reactions section is **Approvable.**

VI **Proposed labeling change related to Overdosage:**

The sponsor proposed inserting the following paragraph under the Overdosage section:

The sponsor submitted 1 article[7] in support of the above paragraph related to Overdosage of Isuprel. A brief review of the article is given in Appendix 2.

Rationale: The above and other five scientific publications[8-11,13] in Appendix 2 provide information regarding cardiotoxicity including myocardial necrosis associated with intravenous isoproterenol infusions during treatment of severe asthma[7-13] and the possibility of enhanced cardiotoxicity of intravenous isoproterenol infusion by the concomitant use of intravenous aminophylline or methyl xanthines[8-11,13] or intravenous corticosteroids[8-11].

Recommendation: In this part of the submission for an insertion of the proposed paragraph in the Overdosage section there is no mention of potentially fatal myocardial necrosis which, for safety reasons, should be mentioned up front {CFR §314.125(b)(6)}. Thus, this part of the submission is **NOT approvable.**

If the sponsor incorporates more accurate (and annotated) information, a paragraph may be inserted, for example, as follows:

VII **Proposed labeling change related to Dosage and Administration:**

The sponsor proposed inserting the following under this section:

Reference articles in Appendices 1 and 2 are reviewed for the evaluation of the dose of intravenous Isuprel to be used in refractory asthma in children, and reference articles in Appendices 1, 2 and 3 for the evaluation of doses of Isuprel to be recommended for pediatric cardiopulmonary resuscitation (CPR) and post-resuscitation stabilization. Reference is also made to a current text book on PALS (Pediatric Advanced Life Support)[17]. The doses reported in these studies are tabulated in Appendix 4.

(1) Dose of intravenous Isuprel for treatment of severe refractory asthma

Rationale: For the proposed dosages of intravenous Isuprel infusions for refractory asthma and for CPR in children, an important concern with the submission is that identical doses of Isuprel are being proposed for different therapeutic uses, and no specific recommendations are made with regard to the amount of incremental doses of Isuprel infusion to be used for treatment of refractory asthma.

In children, treatment of status asthmaticus requires larger doses of intravenous Isuprel infusion and far greater plasma isoproterenol concentrations than those that are used to produce hemodynamic effects[15,16]. Many published studies recommended starting with relatively lower doses of intravenous Isuprel infusion (0.05 to 0.1 μg/min)[1-3,7-9,12-14]. The dose is then recommended to be increased cautiously by 0.2 μg/kg/min every 15 to 20 minutes[2]. Although a maximum dose of 0.5 μg/kg/min has been reported[15] in the treatment of severe reactive airways disease, it is important to remember that fatal ventricular tachycardia[8] has occurred with intravenous Isuprel at a dose of 1.6 μg/kg/min (the maximum dose used in that report being 3.2 μg/kg/min), and that ventricular fibrillation had also been observed with doses as low as 0.2 μg/kg/min[7], and also that ECG abnormalities and cardiac enzyme elevations suggestive of myocardial ischemia have been reported at intravenous Isuprel infusion rates of 0.1 to 0.17 μg/kg/min[7] and at 2.6 μg/kg/min[2]. It is also noteworthy that in one case report, chest pain, ECG changes and CPK-MB elevation had occurred four hours after the Isuprel infusion has been discontinued[10].

Recommendation: There is insufficient information {CFR §314.125(b)(4)} about the dose of Isuprel to determine whether it is safe for use as described in the proposed labeling. Dose-response studies, and pharmacokinetic-pharmacodynamic studies need to be carried out in this population of patients before a dose regimen could be recommended. Thus, this part of the submission for an insertion of the proposed paragraph related to dosage of intravenous isoproterenol recommended for refractory asthma in children in the Dosage and Administration section is **NOT approvable**

(3) Dose of intravenous isoproterenol for pediatric CPR

Rationale: With regard to use of Isuprel injection in CPR, isoproterenol used to be recommended in the treatment of hemodynamically significant bradycardia but is now deleted from most recent manuals of

Pediatric Advanced Life Support (PALS)[17]. Although Isuprel may be effective, it is also a potent vasodilator and can redirect blood away from the viscera and may compromise coronary perfusion by decreasing diastolic pressure. Epinephrine infusions, which do not produce significant vasodilatation, are preferred to intravenous Isuprel infusion in the treatment of hemodynamically significant bradycardia[17].

Recommendation: Here, too, there is insufficient information {CFR §314.125(b)(4)} about the dose of Isuprel to determine whether it is safe for use as described in the proposed labeling. Dose-response studies are lacking. Thus, the submission for an insertion of the proposed paragraph related to recommended dosage of isoproterenol injection for use in pediatric CPR is **NOT approvable.**

SUMMARY

This is a review of a supplemental application on NDA 10-515 submitted by Abbott Laboratories with proposed changes to be made in package insert labeling related to "pediatric use" for ISUPREL injection. The labeling supplements also include revisions to (i) Indications and Usage (1 added), (ii) Warnings (1 added), (iii) Precautions (1 added), (iv) Pediatric Use (1 added), (v) Adverse Reactions (1 added), (vi) Overdosage (1 added), and (vii) Dosage and Administration (2 added) rather than labeling changes confined to the "Pediatric Use Subsection in the Labeling" as alleged in the submission letter.

Following a review of scientific literature related to pharmacokinetics and clinical use of ISUPREL within the context of the proposed labeling changes, the application for the labeling changes is recommended NOT approvable (with the exception of addition to the Adverse Events section of: *"CNS: Nausea, visual blurring, Respiratory: Dyspnea, Other: Pallor"* which is approval). The proposed changes in packet insert labeling with the recommendations are summarized in the Table (see Page 8)

The reasons for non-approval are as follows:

(i) none of the referenced studies was a double-blind, well-controlled clinical study of Isuprel and therefore the application lacks substantial evidence from well-controlled double-blind clinical trials {CFR §314.125(b)(5) and CFR §314.126} of adequate sample size and statistical power to permit objective evaluation of safety and efficacy of isoproterenol under Indications and Usage, and Pediatric Usage sections,

(ii) the proposed labeling changes in the Warnings and Overdosage sections are misleading, there being no mention of the most important adverse report, i.e., potentially fatal myocardial necrosis that has been reported with use of intravenous isoproterenol infusions {CFR §314.125(b)(6)} in many case studies, and

(iii) there is insufficient information {CFR §314.125(b)(4)} (e.g., dose response studies, pharmacokinetic and pharmacodynamic studies) about the dose of the drug to determine whether the drug is safe for use as described in the proposed labeling changes under the Precautions, Adverse Reactions and the Dosage and Administration sections.

/S/

1/23/98

Khin Maung U, MBBS, MMedSc, MD(NSW), MD, FACP

cc: orig.
HFD-110
HFD-110 / CSO / K.M.U

Table: Summary of proposed labeling changes and reviewer's recommendations

Section	Proposed labeling change		Recommendation
Indication and Usage:			NOT approvable
Warnings:			NOT approvable
Precautions:			NOT approvable
Pediatric Use:			NOT approvable
Adverse Reactions:	CNS:	Nausea, visual blurring	
	Respiratory:	Dyspnea	
	Other:	Pallor	Approvable
Overdosage:			NOT approvable
Dosage and Administration:			NOT approvable
			NOT approvable

APPENDIX 1

(1) *Wood DW, Downes JJ, Scheinkopf H, Lecks HI. Intravenous isoproterenol in the management of respiratory failure in childhood status asthmaticus. J Allergy Clin Immunol 1972; 50: 75-81.*

This is a study reported in 1972 involving 19 children in status asthmaticus and respiratory failure who were treated with a continuous infusion of isoproterenol (0.08-2.7 µg/kg/min). Reduction of arterial PCO_2 by ≥10% was observed within a mean interval of 1.8 hours, and by 10.2 hours, the arterial PCO_2 was 48 mmHg or less. Isoproterenol infusion could be discontinued within a mean time of 45 hours. One child failed to respond and required mechanical ventilation; another experienced ventricular tachycardia (at dose of 0.2 µg/kg/min) which subsided promptly without evidence of myocardial damage when the infusion was discontinued.

Comment: Open-label isoproterenol infusion was used in the treatment of life-threatening childhood status asthmaticus. Intravenous isoproterenol carries a risk of cardiac arrhythmia, and there was one child who did not respond. For each individual patient, the physician has to weigh the risks of isoproterenol therapy carefully against that of mechanical ventilation and neuromuscular blockage which may become required in respiratory failure associated with status asthmaticus.

(2) *DeNicola LK, Aboudan K. Resistant Status Asthmaticus in Children. J Florida Med Asso 1990;77(9):809-13.*

This report describes a child who received 5.5 hours of halothane in conjunction with isoproterenol and theophylline intravenously to reverse respiratory failure with profound respiratory acidosis. Halothane did not significantly improve ventilation, and it was associated with significant hemodynamic complications (fall in central venous pressure, blood pressure and prompt cessation of urine output). Cessation of halothane caused a dramatic and immediate improvement in urine output and blood pressure without a relapse into respiratory acidosis.

Comment: Isoproterenol was used intravenously in the treatment of this child with severe childhood status asthmaticus and respiratory failure. However, the focus of the publication was on use of halothane anesthesia for asthma. The authors recommended that as a bronchodilator, halothane may be effective in the operating theater for manipulation-induced bronchospasm. In no other circumstance should halothane be substituted for more traditional therapies.

(3) *Griffith JA, Kozloski GD. Isoproterenol-theophylline interaction: Possible potentiation by other drugs. Clin Pharm 1990; 9:54-7.*

The paper describes a case of drug interactions in a 14-year old asthmatic boy admitted to pediatric critical care unit after shooting himself in the head with a 0.22 caliber firearm (the bullet perforated both frontal lobes.) While on mechanical ventilation, he started wheezing on day 3. He was given 200 mg iv bolus aminophylline followed by an infusion of 0.5 mg/kg/hr, later adjusted to 1.6 mg/kg/hr to maintain serum theophylline concentrations of 10-20 µg/ml. When his bronchospasm persisted, iv isoproterenol (0.1 µg/kg/min) and iv methylprednisolone 40 mg q 6h were administered. The aminophylline requirement rose to a peak infusion rate of 6 mg/kg/hr. When isoproterenol infusion was discontinued, the aminophylline requirements fell abruptly. The patient continued to improve, and was discharged from hospital on Theo-Dur 300 mg q6h po.

Comment: This paper emphasizes the importance of increased clearance of theophylline when the patient is receiving isoproterenol concurrently.

(4) *Victoria MS, Tayaba RG, Nangia BS. Isoproterenol infusion in the management of respiratory failure in children with status asthmaticus: experience in a small community hospital and review of the literature. J Asthma 1991; 28(2): 103-8.*

Of 701 children admitted to Methodist Hospital, Brooklyn, NY during Jan 1985 through Dec 1988, 11 children (8 months to 15 years) went into respiratory failure. All except one patient were successfully treated with intravenous isoproterenol (mean dose 0.3 µg/kg/min, range 0.1 - 0.6 µg/kg/min; mean duration 29 hours, range 10 hr - 5 days) without any complications. Only one patient needed mechanical ventilation.

Comment: This study suggests that intravenous isoproterenol may be useful to avoid the need for mechanical venitlation in a few selective severely asthmatic children going into respiratory failure.

(5) *Escribano Subias J, Sanz Marique N, Morales Hidalgo V, Clofent Vilaplana R, Iglesias Berenguer J, Roqueta Mas J, Eseverri Asin JL. Treatment of status asthmaticus. Experience of intravenous beta-adrenergic bronchodilator therapy in 71 cases. An Esp Pediatr (Spain) 1989; 31(5): 435-9.*

Abstract only available: In a retrospective study of 71 patients admitted for status asthmaticus over 8 years, 67% were IgE dependent asthmatic children and 31% were non-IgE dependent asthmatics. Intermittent positive pressure ventilation was needed in 20 instances; no difference was found between the two types of asthmatics. 33% of IgE dependent children were treated using a continuous IV infusion of hexoprenalina, with 5 (31%) requiring intermittent positive pressure ventilation. The rest received a continuous IV infusion of isoproterenol with only 16% requiring intermittent positive pressure ventilation. The authors found isoproterenol to be more effective than

hexoprenalina in the treatment of status asthmaticus, and that the Downes score was a good predictor-index scoring system in many cases.

Comment: Another study (Spanish) demonstrating usefulness of intravenous isoproterenol in the treatment of status asthmaticus in children.

(6) *Bohn D, Kalloghlian A, Jenkins J, Edmonds J, Barker G. Intravenous salbutamol in the treatment of status asthmaticus in children. Crit Care Med 1984; 12 (10): 892-6.*

In 14 children who had a total of 16 episodes of respiratory failure unresponsive to bronchodilator therapy, the effect of continuous IV infusion of salbutamol was studied. The mean $PaCO_2$ at the start of the infusion was 60±6 torr. A loading dose of 1 µg/kg/min was given over 10 min, followed by an infusion of 0.2 µg/kg/min which was increased in 0.1 µg/kg/min steps according to response. The maximum dose was 4 µg/kg/min. On 11 (69%) occasions, a sustained reduction in $PaCO_2$ was achieved within 4 hours of starting the infusion. In 5 (11%) instances, no reduction in PaCO2 was seen and mechanical ventilation was instituted because of increasing respiratory distress and CO_2 retention. Mean heart rate during the infusion increased from 161 to 183 beats/min. Compared to previous data from 30 pediatric patients who received IV isoproterenol, salbutamol produced less effect on heart rate and a more sustained fall in PaCO2 without the recurrence of bronchospasm. Salbutamol was a safe and effective bronchodilator capable of reversing severe bronchospasm in most children who would otherwise require mechanical ventilation, and its greater specificity for ß-2 receptors makes it preferable to isoproterenol.

Comment: Not a double-blind control study. Intravenous infusion of salbutamol found to be more effective in children with asthma than intravenous isoproterenol infusion in status asthmaticus in children.

APPENDIX 2

(7) *McGuire JF, O'Rouke PP, Colan SD, Geha RS, Crone R. Cardiotoxicity during treatment of severe childhood asthma. Pediatr 1991; 88(6): 1180-6.*

In 20 children 1-18 years old admitted for severe exacerbation of childhood asthma (6 treated with iv isoproterenol infusion and 14 who were not), evidence of cardiotoxicity was detected in all six children treated with iv isoproterenol (marked elevation of serum creatinine phosphokinase isoenzyme (CPK-MB) and ECG abnormalities (depression or elevation of ST-T wave segments) consistent with transient myocardial ischemia). In 3 of these 6 patients, follow up ECGs showed reversion to normal. One patient had severe labile asthma requiring four admissions to this study: during the two admissions when she received iv isoproterenol, her CPK-MB were elevated (47 and 24) with cardiopulmonary arrest in the latter admission; in two other admissions when iv isoproterenol was not given, the CPK-MB was 7 in one and 54 in the other. CPK-MB levels were not correlated with the peak infusion rate or total dose of iv isoproterenol.

Comment: This study demonstrates the importance of ECG monitoring and monitoring of CPK-MB enzymes during intravenous isoproterenol infusions to detect early evidence of cardiotoxicity.

(8) *Kurland G, Williams J, Lewiston NJ. Fatal myocardial toxicity during continuous infusion intravenous isoproterenol therapy of asthma. J Allergy Clin Immunol 1979; 63 (6): 407-11.*

An 18-year old steroid-dependent asthmatic female with respiratory failure (with severe Cushing's syndrome, osteoporosis, amenorrhea, obesity, hypertension, enuresis and renal ljthiasis as co-morbid illnesses, and recent exposure to varicella without skin lesions having developed yet) was treated with continuous intravenous infusion of isoproterenol. Aminophylline, hydrocortisone, aerosolized isoetharine and oxygen were also administered. The patient responded to this therapy with $PaCO_2$ falling from 70 torr to 33 torr in 18 hours. The maximum isoproterenol dosage administered was 0.32 µg/kg/min. 36 hours following the institution of therapy, as isoproterenol was being tapered, the patient experienced an increase in respiratory distress followed by cardiac arrest. Postmortem examination revealed multiple small areas of myocardial necrosis not usually seen in asthma, and were thought to be related to the effects of isoproterenol or the combination of isoproterenol and aminophylline on the stressed, hypoxic myocardium.

Comment: Fatal cardiotoxicity with myocardial necrosis resulted in this patient from treatment with intravenous isoproterenol and/or enhanced cardiotoxic effect due to concomitant use of intravenous aminophylline and intravenous corticosteroids. This study again illustrates the need for ECG and cardiac enzyme monitoring during intravenous isoproterenol infusions in patients with asthma (particularly so because these patients need larger doses than that produce hemodynamic effects).

(9) *Matson JR, Loughlin GM, Strunk RC. Myocardial ischemia complicating the use of isoproterenol in asthmatic children. J Pediatr 1978; 92(5): 776-8.*

A 14-year old boy with perennial, steroid-dependent asthma since early life, and recent hypertension, was admitted for an upper respiratory infection that triggered an episode of asthma not responding to increasing doses of oral steroids and giving subcutaneous epinephrine. Oxygen, intravenous aminophylline and hydrocortisone were given, together with isoproterenol by intermittent positive pressure. When he complained of chest pain, isoproterenol was discontinued and ECGs were found to be normal. 8 hours later, patient developed subcutaneous emphysema (without pneumothorax or pneumomediastinum in chest X-ray) which required stopping all inhalation therapy. As $PaCO_2$ rose from 39 to 45 torr, intravenous isoproterenol therapy was begun with a low starting dose of 0.05 µg/kg/min. After 10 minutes, dyspnea improved, and $PaCO_2$ deceased to 36 torr. As the infusion rate was increased to 0.11 µg/kg/min, his respiratory status improved; his heart rate rose from 120 to 160, and a 12-lead ECG showed ST segment depression and T wave inversions in Leads II, III and aVF after 25 minutes at the above dose. This was interpreted as myocardial ischemia and the infusion was stopped. A repeat ECG 20 minutes later revealed normal ST segments but T waves were flat or biphasic. The patient continued to improve gradually. The ECG on discharge was normal. SGOT, CPK and LDH and isoenzymes were not elevated 24 and 48 hours after the ECG changes.

Comment: This study demonstrates the potential enhancement of cardiotoxicity of intravenous isoproterenol infusion by the concomitant use of intravenous aminophylline and/or intravenous corticosteroids, and the benefit of ECG monitoring which gave guidance regarding when to stop isoproterenol infusions so that the cardiotoxicity (and a potentially fatal arrhythmia or myocardial ischemia) was prevented.

(10) *Mikhail MS, Hunsinger SY, Goodwin SR, Loughlin GM. Myocardial ischemia complicating therapy of status asthmaticus. Clin Pediatr (Phila) 1987; 26(8): 419-21.*

10 year-old boy with 9-year history of asthma had exacerbation of asthma and failed to improved after hospitalization and 3 doses of subcutaneous epinephrine and aerosolized isoetharine. In the pediatric intensive care unit, he was given supplemental oxygen, intravenous hydration, aminophylline (1 mg/kg/min), methylprednisolone (1 mg/kg q6h), and aerosolized isoetharine q 2h. When he became progressively obtunded with persistent CO_2 retention, intravenous isoproterenol was started at 0.1 µg/kg/min, increased by 0.1 µg/kg/min to a maximal dose of 0.7 µg/kg/min, with maximal heart rate of 188 beats/min. Mental status improved rapidly and respiratory acidosis resolved. The isoproterenol infusion was discontinued after 22 hours. Four hours later, the patient complained of crushing substernal chest pain, and ECG showed markedly elevated ST segments over the left precordium. The theophylline level at that time was 14.2 µg/ml. Nitroglycerin 0.2 mg given sublingually relieved the pain. Repeated ECG showed persisting ST-segment elevation in V_5 and V_6. Intravenous nitroglycerin 0.2 µg/kg/min was given with further improvement in the ST-segment. CPK-MB isoenzymes were elevated at 2, 9, and 21 hours, and LDH also increased to a maximum of 374 IU/l with increased LDH_1 and LDH_2 (myocardial LDH). The ECG continued to improve and became normal by 6 days. A gated blood pool scan of the heart showed normal ventricular wall motion and an ejection fraction of 74%.

Comment: This patient had severe myocardial ischemia without infarction even though the isoproterenol infusion had been discontinued 4 hours earlier. He was also receiving intravenous aminophylline and intravenous methylprednisolone which could have enhanced the cardiotoxicity of intravenous isoproterenol. This again highlights the need for cardiac monitoring, supplemental oxygen during intravenous isoproterenol therapy for treatment of severe refractory asthma.

(11) *Page R, Gay W, Friday G, Fioreman P. Isoproterenol-associated myocardial dysfunction during status asthmaticus. Ann Allergy 1986; 57(6): 402-4.*

17-year old female with 11-year history of asthma was hospitalized for severe wheezing. After subcutaneous epinephrine and aerosol isoetharine and aerosol isoproterenol therapy, and intravenous aminophylline and intravenous methylprednisolone therapy were not effective, she was admitted to the intensive care unit and started on intravenous isoproterenol infusion at 0.1µg/kg/min. Due to persistent hypercarbia ($PaCO_2$ = 72 torr), intravenous isoproterenol was increased rapidly in hourly increments over 6 hours to 2.5 µg/kg/min at which dose the $PaCO_2$ decreased to 40 torr. The isoproterenol infusion was decreased sequentially to 0.1 µg/kg/min. At 30 hours after admission, the patient became agitated, unresponsive to verbal commands, and developed eye-blinking and tonic clonic activity of her right arm which lasted a few minutes. Isoproterenol was stopped, lactated Ringer's, sodium bicarbonate and Dilantin were given. Within 1 hour, the patient was orientated and verbalizing appropriately. Over the next few hours, she developed chest pain, dizziness, tachycardia, and became hypotensive. with cool extremities, poor capillary refill and a palpable liver 3 cm below the costal margin. Dobutamine was begun. Chest X-ray revealed cardiomegaly. EKG revealed marked ST-T elevation in the left precordial leads and mild elevation of Lead II and AVF consistent with infero-lateral wall ischemia. CPK-MB isoenzymes measured for the next 48 hours were all normal. A 2D and M-Mode echocardiogram showed decreased left ventricular function with a shortening fraction of 0.13 (normal > 0.28). As the blood pressure and perfusion gradually improved, dobutamine was stopped 4 hours later. The next morning, the ischemic changes on her ECG had resolved. Subsequent chest X-rays documented rapid resolution of the pulmonary edema with subsequent resolution of her cardiomegaly. An echocardiogram on day 6 revealed normal chamber dimensions and shortening fraction of 0.33. She was discharged on hospital day 8 with no evidence of cardiopulmonary disease apart from her chronic asthma.

Comment: This patient had reversible myocardial ischemia without infarction and heart failure when though the isoproterenol infusion had been continued for about 30 hours. She was also receiving intravenous aminophylline and intravenous methylprednisolone which could have enhanced the cardiotoxicity of intravenous isoproterenol. This case report highlights the need for cardiac monitoring, and suggests that timely withdrawal of intravenous infusion of isoproterenol was associated with reversal of heart failure and reversal of evidence of ischemic changes.

(12) *Baker L, Snow J, Pomposiello G, et al: Isoproterenol-induced "coronary steal" Metabolic observations in human coronary artery disease (CAD), Clinical Research 1969; 17: 228.*

(13) *Nicklas RA, Whitehurst VE, Donohoe RF. Combined use of beta-adrenergic agonists and methyl xanthines. N Engl J Med 1982; 307: 556-7 [Letter].*

These authors from the Food and Drug Administration cited a recent FDA Drug Bulletin on "Interactions between methyl xanthines and beta adrenergic agonists" and emphasized the need for awareness of adverse cardiac effects (ventricular tachyarrhythmias frequently culminating in ventricular fibrillation and sudden death, associated with well-defined areas of myocardial necrosis under histological examination) of ß-adrenergic agonist enhanced by the concomitant administration of methyl xanthines such as aminophylline and theophylline. They proposed the possibility of a subgroup of patients with asthma who are at increased risk when receiving both ß-adrenergic agonists and methyl xanthines, and advised careful cardiac monitoring and autopsy examination where available.

Comment: This study further emphasizes the importance of cardiac monitoring when ß-agonists are used together with methyl xanthines.

APPENDIX 3

(14) *Zaritsky A, Chernow B. Use of Catecholamines in pediatrics. J Pediatr 1984; 105(3): 341-50.*

This review article presents guidelines for the use of catecholamines in the pediatric patient based on current understanding of pediatric cardiovascular physiology and adrenergic receptor physiology. The article mentions that little information is available about age-related responses in the developing child.

Catecholamine therapy based on studies in adults is not necessarily applicable to the child or infant, because of differences in cardiovascular and adrenergic physiology. For example, the stroke volume in a newborn infant (1.5 ml/kg) has a limited capacity to increase because of diminished ventricular diastolic compliance. Consequently, ventricular end diastolic volume does not increase without significant elevation of filling pressure. Cardiac output equals stroke volume times heart rate, and stroke volume is relatively fixed; thus, the cardiac output in premature and small infants is heart rate dependent. In these patients, increasing the heart rate with a chronotrope such as isoproterenol increases cardiac output. With advancing age, cardiac output rises, heart rate falls, and stroke volume increases markedly.

Animal studies showed a diminished contractile and vascular response in the neonate to exogenous catecholamines. However, the neonatal heart may be functioning at near capacity, limiting the ability to demonstrate further increases in contractility in response to exogenous catecholamines. These animal studies suggest that pediatric patients are less responsive to exogenous catecholamines than are adults.

There are differences in adrenergic receptor ontogeny among different species. The sympathetic nervous system is immature at birth in many species. The time course of myocardial sympathetic nervous system innervation in humans is not known. In puppies, increased contractility in response to dopamine was associated with advancing age and corresponded to the growth of sympathetic nerves into the ventricle.

The peripheral vascular effects of isoproterenol in young animals are less than those in adults and increase with age. Pulse pressure widens through an increase in systolic and a decrease in diastolic blood pressure. As heart rate and contractility increase, myocardial oxygen consumption rises, but oxygen delivery to the heart through coronary flow may decrease as a result of the drop in diastolic blood pressure and shortened diastolic filling time. Cardiac output increases as long as circulating blood volume is adequate, although the change maybe small in young patients. In adults, isoproterenol causes proportionately less blood flow to the splanchnic bed and more to the skeletal muscle, an effect less pronounced in children.

Isoproterenol is a potent pulmonary vasodilator and bronchodilator, making it useful in reactive pulmonary artery hypertension and in status asthmaticus. However, careful cardiac monitoring (including monitoring of rhythm, QTc) and arterial blood gas monitoring are required, and oxygen should always be administered during isoproterenol

infusions in patients with asthma. This is because of the risks of ventricular arrhythmias, myocardial ischemia and an increase in intrapulmonary shunting with a resultant fall in oxygen tension despite less bronchospasm. Angina and myocardial infarction have been reported in pediatric patients.

The half-life of isoproterenol is 1.5 minutes.

(15) *Reyes G, Schwartz PH, Newth CJ, Eldadah MK. The pharmacokinetics of isoproterenol in critically ill pediatric patients. J Clin Pharmacol 1993; 33(1): 29-34.*

Pharmacokinetics of isoproterenol (ISO) was studied in two groups of pediatric intensive care unit patients: postoperative cardiac patients (POC, n=10), and reactive airway disease patients (RAD, n=9). There were 12 male and 7 female patients, their ages ranging from 2 days to 14 years. The average ISO dosing rate was 0.30 (range = 0.01 to 5.5) µg/kg/min for the whole study population. The POC patients received a significantly (P<0.0001) lower dosing rate than RAD patients (0.029±0.002 vs 0.50±0.21 µg/kg/min); the average steady-state plasma concentrations of ISO were also lower in the POC patients (1.3±0.3 vs 13.9±4.9 ng/ml; P<0.0001). The steady-state plasma concentration, normalized to a dosing rate of 0.05 µg/kg/min was 1.9±0.3 ng/ml for all patients, and the clearance was 42.5±5.0 mg/kg/min. Postoperative cardiac patients had a significantly higher normalized steady-state plasma concentration and a relatively lower clearance than did RAD patients (2.1±0.3 vs 1.7±0.4 ng/ml, P<0.05; and 33.3±4.9 vs 48.4±7.3, P<0.06, respectively). The average plasma half-life of ISO was 4.2±1.5 minutes, and the volume of distribution was 216±57 mg/kg. The apparent higher clearance of ISO in RAD patients may be related to an improved perfusion status relative to the POC patients or to a possible influence of nonlinear pharmacokinetics.

Comment: This study suggests that the pharmacokinetics of intravenous isoproterenol infusions in children is highly variable and may vary with serum concentration and the disease state in which isoproterenol infusions are used.

(16) *Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children. Inotropes and vasopressors. Clin Pharmacokinet 1994; 27(5): 345-67.*

In this review article, the authors mentioned the variation in dose of isoproterenol in the treatment of bradyarrhythmias compared to that of bronchial hyper-reactivity in which higher doses of isoproterenol are required (similar to article #21 reviewed above). They also cautioned about the risk of life-threatening complications including atrial or ventricular dysrhythmias and myocardial ischemia (even in the absences of coronary artery disease) associated with use of isoproterenol in the treatment of reactive airways disease which requires far greater plasma isoproterenol concentrations than those that cause hemodynamic effects. Thus, while isoproterenol remains a useful drug for the treatment of severe life-threatening asthma in young children and for the treatment of bradycardia in all age groups, more specific β_2-agonists are now preferred for the treatment of reactive airway disease.

The $t_{1/2}$ of isoproterenol in plasma is given as 1.5-4.2 minutes. Its principle route of elimination is methylation by COMT to 3-*O*-methyl-isoproterenol, which is then excreted into the urine and bile in its free or conjugated form. A second route of removal is uptake by the extraneuronal uptake system (uptake-2)

(17) *1992 National Conference on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC). Part III. Adult ACLS. JAMA 1992; 268 (16): 2199-2241; Part VI. Pediatric ALS. Ibid p. 2262-75.*

The Section on "*Bradycardia Treatment Algorithm*" describes use of isoproterenol as follows:-

"Isoproterenol hydrochloride continues in disfavor for patients with severe symptomatic bradycardia. Isoproterenol produces negative effects of increased myocardial oxygen consumption and peripheral vasodilatation; its only positive effect is to provide chronotropic support. Isoproterenol requires a delicate risk-benefit balance; patients who are ill enough to need isoproterenol are probably too ill to tolerate it. Isoproterenol should be used, if at all, with extreme caution and probably only by experienced clinicians in an intensive care setting. At low doses in patients with a pulse it is a Class IIb (possibly helpful) intervention; at all other doses it is a Class III (harmful) intervention."

Isoproterenol was not one of the drugs recommended for bradyarrhythmias in Pediatric ALS, and it is no longer included in the list of "Drugs used in pediatric advanced life support".

Appendix 4

Dose of intravenous isoproterenol infusion reported in referenced studies

Ref	Clinical Use	Patient	Dose (intravenous)	Response
1.	Status asthmaticus	19 children, 16 mo -15 yr	0.08 - 2.7 µg/kg/min x 45 hours	one failed; one developed VT at 2 µg/kg/min
2.	Respiratory failure	1 child, 12 year old	0.1 µg/kg/min, increased by 0.2 µg/kg/min q 15 min up to 1.3 µg/kg/min, IPPV, inhaled halothane	ST depression by 4 mm at iv infusion rate of 2.6 µg/kg/min
3.	Asthma, on Ventilator	1 child 14 year old	0.1 µg/kg/min	caused increased clearance and decreased blood levels of theophylline
7.	Respiratory failure	20 children, 1-18 year	0.1-0.17 µg/kg/min, increased q 20 min to heart rate > 200/min	All patients on isoproterenol developed ECG ECG changes & elevated CPK-MB enzyme)
8.	Respiratory failure	1 child, 18 year	0.1 µg/kg/min to maximum of 0.32 µg/kg/min	Died: ventricular fibrillation (1.6 µg/kg/min) Autopsy showed myocardial necrosis.
9.	Respiratory failure	1 child, 14 year	0.05 µg/kg/min, increased to 0.11 µg/kg/min	Pt had ECG changes and elevated CPK-MB
10.	Respiratory failure	1 child, 10 year	0.1 µg/kg/min, incr by 0.1 µg/kg/min to a maximum of 0.7 µg/kg/min (HR = 188/min)	Pt had chest pain, ECG changes, elevated CKP-MB 4 hrs after stopping isoproterenol
11.	Respiratory failure	1 child, 17 year	0.1 µg/kg/min, increased to 2.5 µg/kg/min	Dev. chest pain, cardiomegaly and CHF at 30th hour, resolved completely
14.	Review Article		Recommend 0.05 - 1.0 µg/kg/min	supplemental O2, cardiac & ABG monitoring
15.	Critically ill patients	10 postop. cardiac pts 9 asthma patients	Postop. cardiac pts: 0.029±0.002 µu/kg/min Asthma patients: 0.50±0.21 µg/kg/min	Asthma patients require larger doses than post-op cardiac patients

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 10515/S022

CHEMISTRY REVIEW(S)

MAR 1 1999

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 10-515 **Review #:** 2 **REVIEW DATE:** February 23, 1999

SUBMISSION	DOC DATE	CDER DATE	ASSIGNED DATE
Supplement SLR-022	12/31/97	1/5/98	1/6/98
Supplement SE1(~~AF~~BF)-022	2/5/99	2/9/99	2/16/99

NAME & ADDRESS OF APPLICANT:
Abbott Laboratories
200 Abbott Park Road, D-389 AP30
Abbott Park, IL 60064

DRUG PRODUCT NAME:

Proprietary: Isoprel
Nonproprietary/USAN: Isoproterenol Hydrochloride Injection, USP
Code Name/#:
Chem.Type/Ther.Class: 1S

PHARMACOL.CATEGORY/INDICATION: bronchodilator and heart blood flow stimulant

DOSAGE FORM: injection
STRENGTHS: 1:50
ROUTE OF ADMINISTRATION: injection

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See next page.

RECORDS AND REPORTS CURRENT: yes

SUPPLEMENT PROVIDES FOR revised labeling adding information related to the pediatric population as required under section 505(b) of the Federal Food, Drug and Cosmetic Act.

REMARKS/COMMENTS:
Changes in package insert do not pertain to chemistry. Description and How Supplied sections are adequate.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval for this supplement in regard to chemistry.

/S/

Carl J. Berninger, Ph.D., Review Chemist

copies:
Orig. NDA
HFD-110/Division File
HFD-110/CBerninger
HFD-110/GBuehler

/S/ 2-26-99

R/D Init by: K. Srinivasachar

File Name: c:\sup-rev\10515s22b.doc

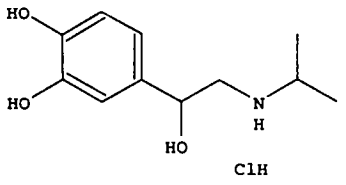
STRUCTURE

BD Number:
0007818AA

CAS Number:
000051309

Formula:
C(11)H(18)NO(3)Cl

Weight:
247.50



NAME:
ISOPROTERENOL HYDROCHLORIDE

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DF

FEB 6 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: ~~10-515~~

REVIEW DATE: February 3, 1998

SUBMISSION	DOC DATE	CDER DATE	ASSIGNED DATE
Supplement ~~SLR~~ SE1-022	12/31/97	1/5/98	1/6/98

NAME & ADDRESS OF APPLICANT:
Abbott Laboratories
200 Abbott Park Road, D-389 AP30
Abbott Park, IL 60064

DRUG PRODUCT NAME:

Proprietary: Isoprel
Nonproprietary/USAN: Isoproterenol Hydrochloride Injection, USP
Code Name/#:
Chem.Type/Ther.Class: 1S

PHARMACOL.CATEGORY/INDICATION: bronchodilator and heart blood flow stimulant

DOSAGE FORM: injection
STRENGTHS: 1:50
ROUTE OF ADMINISTRATION: injection

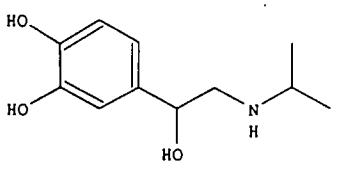
STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

BD Number:
0007818AA

CAS Number:
000051309

Formula:
C(11)H(18)NO(3)Cl

Weight:
247.50



NAME:
ISOPROTERENOL HYDROCHLORIDE

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RECORDS AND REPORTS CURRENT: yes

SUPPLEMENT PROVIDES FOR: changes in the package insert labeling for the subject drug.

REMARKS/COMMENTS:
Changes in package insert do not pertain to chemistry. Description and How Supplied sections are adequate.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval for this supplement as far as chemistry is concerned.

/S/

Carl J. Berninger, Ph.D., Review Chemist

cc:
Orig. NDA
HFD-110/Division File
HFD-110/CBerninger February 3, 1998
HFD-110/GBuehler

R/D Init by: J. Short

File Name: c:\sup-rev\10515s22.doc

/S/
2/6/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 10515/S022

ADMINISTRATIVE DOCUMENTS

MAY 5 1999

LABELING REVIEW

NDA 10-515/S-022 Isuprel (isoproterenol Hydrochloride) Injection

Sponsor: Abbott Laboratories
Hospital Products Division
Abbott Park, IL 60064-3537

Date of Original Submission: December 31, 1997

Date of Not Approvable Letter: September 15, 1998

Date of FPL Submission: April 9, 1999

BACKGROUND

The supplemental application was originally submitted in response to the December 13, 1994 Federal Register statement relating to revision of the Pediatric Use section of the labeling. The firm submitted data supporting the additional indication of treatment o

Drs. U and Fenichel (see Application Review dated April 7, 1998) reviewed the application. Dr. U found the application lacked substantial evidence from well-controlled, double-blind clinical trials to permit an evaluation of the safety and efficacy of the treatment and recommended not approval. Dr. Fenichel agreed, but thought that in the spirit of the pediatric initiative, some useful information could be added to the labeling to assist the physician in deciding whether this drug would be useful in this serious condition. He drafted a paragraph for the Pediatric Use section that described the clinical use of Isuprel Injection in

The package was forwarded to Dr. Temple for signature. He made further revisions to the labeling, emphasizing the adverse consequences that may result if Isuprel is used for this condition. A labeling draft was prepared to accompany the not approvable letter. Dr. Temple signed the letter on September 15, 1998.

The firm originally responded to the letter on February 5, 1999 with FPL. Upon review, however, it was discovered that the first sentence of the revision stated that "Safety and efficacy of isoproterenol in pediatric patients have been established" instead of "have not been established." The firm was contacted, and stated that they would resubmit the FPL. Revised FPL was submitted on April 9, 1999. The following statement was added to the **Pediatric Use** subsection of the **PRECAUTIONS** section of the labeling:

> 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.

The labeling was reviewed and found to be in accordance with the approvable letter dated September 15, 1998. An approval letter will be drafted for Dr. Temple's signature.

/S/ 4/19/99

Gary Buehler
Project Manager

Orig NDA, HFD-110, HFD-110 GBuehler, HFD-110 SBenton

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APR 7 1998

APPLICATION REVIEW

NDA 10-515/S-022 Isuprel (isoproterenol hydrochloride) Injection

Sponsor: Abbott Laboratories
Hospital Products Division
Abbott Park, IL 60064-3537

Date of Submission: December 31, 1997

BACKGROUND

The application was originally submitted on December 31, 1997 and provided for the addition of the following two new indications:

A user fee did not accompany the submission. After conferring with the user fee group, it was determined that the application as submitted would require a fee. If, however, the first indication (tilt testing) was deleted, a fee would not be required because of the change in the user fee regulation exempting new indications that were exclusively pediatric.

The firm was informed of the user fee requirement; they withdrew the

The application, now providing for only the treatment of
with accompanying warnings and precautions and the addition of a few adverse events (nausea, visual blurring, dyspnea and pallor), was reviewed by Dr. U. He found that the application lacked substantial evidence from well-controlled, double-blind clinical trials to permit an objective evaluation of the safety and efficacy of Isuprel for the proposed indication and recommended not approval.

Upon secondary review, Dr. Fenichel agreed with Dr. U's assessment. He did believe, however, that there was some merit to the information submitted, and that it would be of value for it to appear in the labeling as long as that the reader was provided with all of information needed to make an informed judgement as to whether it would be of value. He drafted a paragraph for inclusion in the **Pediatric Use** section of the labeling that provides instructions for use, precautions and warnings (See Dr. Fenichel's memo dated 3/9/98). It was recognized that the inclusion of information of this type in the labeling for approved drugs was a departure from the norm, but the feeling was that the spirit of the pediatric initiative was to provide information that could be useful in the treatment of pediatric patients in the labeling where it was readily accessible.

ACTION

A not approvable letter will be drafted for Dr. Temple's signature. The letter will request, however, that a paragraph describing the use of Isuprel Injection in the treatment of
be added to the **Pediatric Use**

section of the labeling. It will also request that "nausea, visual blurring, dyspnea and pallor" be added to the **ADVERSE REACTIONS** section of the labeling.

/S/

Gary Buehler
Project Manager

4/7/98

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 10515/S022

CORRESPONDENCE

DF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 10-515/S-022

SEP 15 1998

Abbott Laboratories
Hospital Products Division
Attention: Ms. Jill N. Sackett
D-389, Bldg. AP30
200 Abbott Park Drive
Abbott Park, IL 60064-3537

Dear Ms. Sackett:

Please refer to your December 31, 1997 supplemental new drug application 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 January 21, 1998.

The user fee goal date is January 5, 1999.

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 of the labeling. It also provides for the additional indication of the treatment of s

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

To provide some information relating to the use of isoproterenol injection in refractory pediatric asthma, we ask that the following be added as a **Pediatric Use** section of the labeling:

> 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.

In addition, please add "nausea, visual blurring, dyspnea and pallor" to the **ADVERSE REACTONS** section of the labeling as originally proposed.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental 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.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
Telephone: (301) 594-5332

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research