CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

10-515/S024

Trade Name: Isuprel®

Generic Name: isoproterenol hydrochloride

Sponsor: Hospira, Inc.

Approval Date: 7/18/2001

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.

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APPLICATION NUMBER:

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APPLICATION NUMBER:

10-515/S024

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 10-515/S-024

Abbott Laboratories
Attention: Lisa K. Zboril
D-37K, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

Dear Ms. Zboril:

Please refer to your supplemental new drug application dated June 29, 2001, received July 2, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isuprel® (isoproterenol hydrochloride) Injection, 1:5000, 1 mL fill in 1 mL ampul and 5 mL fill in 5 mL ampul.

This "Changes Being Effected" supplemental new drug application provides for an alternate supplier, (b) (4), of the drug substance isoproterenol hydrochloride.

We have completed the review of this supplemental application, and it is approved. Please note for future reference that such changes are generally submitted in a prior approval supplement. Please update the stability information for drug product made using the new source of the drug substance in general correspondences to the NDA after 3 and 6 months' data are available.

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, call Edward Fromm, Regulatory Project Manager, at (301) 594-5313.

Sincerely,

{See appended electronic signature page}

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I for the
Division of Cardio-Renal Drug Products, (HFD-110)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Kasturi Srinivasachar

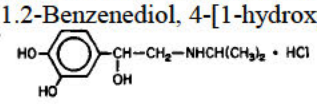
7/18/01 06:41:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S024

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 10-515
3. Name and Address of Applicant (City & State) Abbott Hospital Products Division, Abbott Laboratories D-37K. Bldg. AP30, 200 Abbott Park Road, Abbott Park, Illinois 60064-6157		4. Supplement(s) Number(s) Date(s) SCM-024 June 29, 2001
5. Drug Name Isuprel	6. Nonproprietary Name Isoproterenol Hydrochloride	7. Amendments & Other (reports, etc) - Dates
8. Supplement Provides For: Changes Being Effected An alternate supplier [redacted] (b) (4) of the the drug substance isoproterenol HCl.		
9. Pharmacological Category For mild and transit episodes of heart attack that do not require electrical shock or pacemaker therapy	10. How Dispensed [X] Rx.) [ ] OTC	10. Related IND(s)/ NDA(s)/DMF(s) DMF [redacted] (b) (4) Type II API
12. Dosage Form(s) Injectable	13. Potency(ies) 1:5000, 1 ml in 1 ml ampoule 5 ml in 5 ml ampoule	
14. Chemical Name and Structure 1.2-Benzenediol, 4-[1-hydroxy-2-[(1-methylethyl)-amino]-, hydrochloride 		15. Records/Reports Current Reviewed Yes X Yes X No

15. Comments

Such changes as provided for in S-024 generally call for a prior approval supplement. However because of a drug shortage (this drug is deemed medically necessary) an agreement was reached with the Clinical Division to submit this supplement as a CBE with the understanding that Abbott would not implement the change until they were informed it was all right to do so by the Agency.

EER Acceptable for the drug substance supplier [redacted] (b) (4) and for drug product manufacturer Abbott Laboratories, McPherson, KS. Ownership of NDA 10-515 was transferred to Abbott Laboratories, Inc in 1997. The McPherson, KS facility has manufactured the drug product since 1977-1978.

[redacted] (b) (4) states that the API was manufactured in accordance with cGMP and as described in DMF [redacted] (b) (4) that was Reviewed by KJongedyk and found adequate. See review of DMF [redacted] (b) (4) dated July 12, 2001.

Abbott Laboratories will test each lot of the API prior to use in manufacturing the drug product to demonstrate that all USP tests and specifications are meet for Isoproterenol Hydrochloride USP.

Recommendations and Conclusions
An approval letter should be issued with a note such changes are usually prior approval supplements.

18. REVIEWER		
Name Kathleen E. Jongedyk	**Signature**	**Date Completed July 12, 2001**

Distribution: Original Jacket x Reviewer x Division File x CSO x File name desktop10-515Abbott

REVIEW NOTES

DRUG SUBSTANCE

(b) (4)

[redacted]

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

9- **STABILITY**

P 206

Abbott provides the same stability protocol for both ampoule fills the 1 m fill in 1 ml ampoule and 5 ml fill in 5 ml ampoule one study for each fill volume for.

Drug product formulation each ml of solution contains: 200 µg Isoproterenol Hydrochloride, USP, 0.12 mg Lactic Acid, USP, 7.0 g Sodium Chloride, USP, 1.8 g Sodium Lactate USP, 1.0 mg Metabisulfite, NF and Water for Injection USP. The pH is adjusted to 2.4-4.5 with Hydrochloric acid, NF.

1- **Stored at 8-15° C for 24 months, test intervals of initial, 3, 6, 9, 12, 18, and 24 months.**
Stored at 40° C/75%RH for 6 months , test intervals of initial, 1, 2, 3, and 6 months.

2- Tests and test data for
description (colorless to practically colorless liquid)
pH (3.5-4.5)
Isoproterenol hydrochloride (100 - 230 µg/ml)
Isoproterenol hydrochloride label Claim (90.0- 115.0%)
Sodium Metabisulfite
Color and Clarity (clear and colorless or NMT absorbency than Standard)
Clarity of Solution (clear)
Particulate matter
Sterility (meets USP Requirements)
Bacterial Endotoxins (NMT 350 EU/mg Isoproterenol HCl)

3- Data were reported for the initial time, which was assumed to be the QC release test values for the drug product and for the first months storage at 40°C/75%RH

Evaluation: in sufficient stability data reported only initial data only for the 8-15°C storage and one month data for 40°C/75%RH.

PP 207-209 for one-month storage at 40°C/75%RH the assay potency decreased indicating API loss and sensitivity to heat.
1-For the 1-ml fills in 1-ml ampoules from 214 µg/ml (initial) to 197 µg/ml
2-For the 5 ml fill in 5-ml ampoules from 226 µg/ml (initial) to 204 µg/ml.
Stability protocol 8-15° C(24m), 40°C/75%RH (6 m) Only initial and
1-m data reported for 40C/75%RH . This data showed the assay value µg/ml had decreased from114% to 97%.

The 8-15°C indicates storage is a refrigerator under cool place conditions. However ICH Guidelines QIA defines refrigerated conditions as 5 ±3°C. Request Abbott to identify the intended storage place for 8-15°C. NDA 10-515 storage recommended storage statement store in a cool place protect from light that was

revision to store between 8-15°C.

ICH Guidelines include Q1A Stability testing of new drug substances and products provides for ambient humidity as acceptable for drug product such as liquids stored in containers impermeable to water loss such as the glass ampoule. In addition the ICH Guideline provides for drug products intended to be stored at refrigerator temperature to be tested following storage under accelerated conditions of 25°C/60%RH and long term conditions of 5 ± 3°C. NDA 10515 was approved in the 1970s when ICH guidelines did not exist. The necessity of Abbott Laboratories to perform testing at conditions of 25°C/60%RH as well as at long term conditions of 5 ± 3°C could be questionable.

P 2 Post stability commitment to place on stability the first three (3) production batches of Isuprel® 1:5000, 1 ml fill in 1 ml ampoule and 5 ml in 5 ml ampoule stored at 8-15°C and tested at initial, 3, 6, 8, 12, and 24 months. Yearly thereafter to add to the stability program at least one production lot of Isuprel ® 1:5000, 1 ml fill in 1 ml ampoule and 5 ml in 5 ml ampoule and to reported data in the annual reports. Abbott Laboratories commits to continue the stability studies for the exhibit lots provided in NDA 10-515/S-024 and submit these data in the annual reports.

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Evaluation: Post stability commitment is acceptable The commitment meets the requirements in the Stability Guidelines. A change in the API supplier with no change in the specification requirements for a USP API and Abbott Laboratories specifications would not be expected to effect the stability of the drug product.

A- INVESTIGATIONAL FORMULATIONS N/A

B- ENVIRONMENTAL ASSESSMENT No information provided. The same site of manufacturer will be used for the drug product with no expected increase in the amount of API release to the environment,

C- METHOD VALIDATION not required since no changes were made the methods.

D- LABELING No changes made in the labeling.

E- ESTABLISHMENT INSPECTION

Compliance provided acceptable EERs on July 10, 2001 for the API made at (b) (4) (b) (4) **and for the drug product made at Abbott Laboratories, 1776 North Centennial Drive, McPherson KS.**

Tel. July 9, 2001 FDA pre approval NDA coordinator Shirley Berryman FDA Kansas District (913-752-2108) FDA inspector Jim Giefer (314-645-1167.) Jim Giefer inspected Abbott Laboratories McPherson , Kansas site for (b) (4) drug product in March 21-23/01 followed by an inspection by the Division of Biological Drug Product. For FDA drug approval and cGMPs inspection the facility was issued a 483 but no warning letter and is consider in substantial compliance with the cGMPs. This is a large facility manufacturing 10-15 drug product. For FDA Biological drug product inspection concerns were raised about cracked glass vials. NDA 10-515 drug product is packaged in glass ampoules. Mr. Jim Giefer stated that the problem of cracks in glass vial would not apply to the ampoules since Abbott did a 100 percent leak testing of all glass ampoules . All ampoules are placed into a chamber containing methylene blue dye, the chamber is pressurized for a specific time interval, then the ampoules are removed, washed, and inspected for any blue color inside denoting a leak in that ampoule.

17-JUL-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 10515/024**
Stamp: **02-JUL-2001** Regulatory Due: **02-JAN-2002**
Applicant: **ABBOTT LABS**
200 ABBOTT PARK RD D37K AP30
ABBOTT PARK, IL 600646157

Priority: **3P** Org Code: **110**
Action Goal: District Goal: **28-NOV-2001**
Brand Name: **ISUPREL (ISOPROTERENOL HCL) 1:5000 INJ**
Established Name:
Generic Name: **ISOPROTERENOL**
Dosage Form: **INJ (INJECTION)**
Strength: **1:5000**

FDA Contacts: **K. JONGEDYK (HFD-110)** **301-594-5300 , Review Chemist**
K. SRINIVASACHAR (HFD-110) **301-594-5376 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 12-JUL-2001 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 10-JUL-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1925262**
ABBOTT LABORATORIES
1776 NORTH CENTENNIAL DR
MCPHERSON, KS 67460

DMF No:
AADA No:

Profile: (b) (4) OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **10-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE RELEASE TESTER

Establishment: (b) (4)

DMF No: (b) (4)
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **11-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

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

/s/

Kathleen Jongedyk
7/17/01 03:53:08 PM
CHEMIST

Kasturi Srinivasachar
7/18/01 06:36:05 PM
CHEMIST