CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75160

APPROVAL LETTER

ANDA 75-160

JUL 6 1998

Abbott Laboratories
Hospital Products Division
Attention: Thomas F. Willer, Ph.D.
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

Dear Sir:

This is in reference to your abbreviated new drug application dated June 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Metoprolol Tartrate Injection USP, 1 mg/mL (5 mL Ampule).

Reference is also made to your amendments dated January 30, April 17, and May 12, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Metoprolol Tartrate Injection USP, 1 mg/mL (5 mL Ampule) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lopressor® Injection, 1 mg/mL of Novartis Pharmaceuticals Corporation).

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising,

and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

7-6-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75160

DRAFT FINAL PRINTED LABELING

METOPROLOL TARTRATE INJECTION, USP

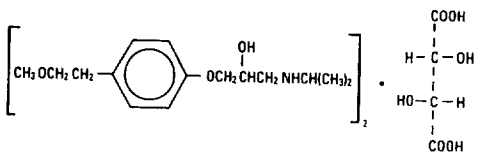
JUL 16 1998

APPROVED

DESCRIPTION

Metoprolol tartrate injection is a sterile solution containing metoprolol tartrate, a selective beta$_1$-adrenoreceptor blocking agent, available in 5 mL ampuls for intravenous administration. Each ampul contains a sterile solution of metoprolol tartrate USP, 5 mg and sodium chloride USP, 45 mg. Metoprolol tartrate is (±)-1-(isopropylamino)-3-[*p*-(2-methoxyethyl) phenoxy]-2-propanol (2:1) *dextro*-tartrate salt, and its structural formula is:

RAO 5809 -R1-Rev. April, 1998



Metoprolol tartrate is a white, practically odorless, crystalline powder with a molecular weight of 684.83. Its molecular formula is $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

CLINICAL PHARMACOLOGY

Metoprolol tartrate is a beta-adrenergic receptor blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on $beta_1$ adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, metoprolol also inhibits $beta_1$ adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have confirmed the beta-blocking

activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Relative $beta_1$ selectivity has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective ($beta_1$ plus $beta_2$) beta blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta blockade. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

In a large (1,395 patients randomized), double-blind, placebo-controlled clinical study, metoprolol was shown to reduce 3-month mortality by 36% in patients with suspected or definite myocardial infarction.

Patients were randomized and treated as soon as possible after their arrival in the hospital, once their clinical condition had stabilized and their hemodynamic status had been carefully evaluated. Subjects were

ineligible if they had hypotension, bradycardia, peripheral signs of shock, and/or more than minimal basal rales as signs of congestive heart failure. Initial treatment consisted of intravenous followed by oral administration of metoprolol tartrate or placebo, given in a coronary care or comparable unit. Oral maintenance therapy with metoprolol or placebo was then continued for 3 months. After this double-blind period, all patients were given metoprolol and followed up to 1 year.

The median delay from the onset of symptoms to the initiation of therapy was 8 hours in both the metoprolol and placebo treatment groups. Among patients treated with metoprolol, there were comparable reductions in 3-month mortality for those treated early (≤8 hours) and those in whom treatment was started later. Significant reductions in the incidence of ventricular fibrillation and in chest pain following initial intravenous therapy were also observed with metoprolol and were independent of the interval between onset of symptoms and initiation of therapy.

The precise mechanism of action of metoprolol in patients with suspected or definite myocardial infarction is not known.

In this study, patients treated with metoprolol received the drug both very early (intravenously) and during a subsequent 3-month period, while placebo patients received no beta-blocker treatment for this period. The study thus was able to show a benefit from the overall metoprolol regimen but cannot separate the benefit of very early intravenous treatment from the benefit of later beta-blocker therapy. Nonetheless, because the overall regimen showed a clear beneficial

effect on survival without evidence of an early adverse effect on survival, one acceptable dosage regimen is the precise regimen used in the trial. Because the specific benefit of very early treatment remains to be defined however, it is also reasonable to administer the drug orally to patients at a later time as is recommended for certain other beta blockers.

Pharmacokinetics

Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. The systemic availability and half-life of metoprolol tartrate in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Following intravenous administration of metoprolol tartrate, the urinary recovery of unchanged drug is approximately 10%. When the drug was infused over a 10-minute period, in normal volunteers, maximum beta blockade was achieved at approximately 20 minutes. Doses of 5 mg and 15 mg yielded a maximal reduction in exercise-induced heart rate of approximately 10% and 15%, respectively. The effect on exercise heart rate decreased linearly with time at the same rate for both doses, and disappeared at approximately 5 hours and 8 hours for the 5 mg and 15 mg doses, respectively.

Equivalent maximal beta-blocking effect is achieved with oral and intravenous doses in the ratio of approximately 2.5:1.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of metoprolol tartrate caused a reduction in heart rate, systolic blood pressure, and cardiac output. Stroke volume, diastolic blood pressure, and pulmonary artery end diastolic pressure remained unchanged.

INDICATIONS AND USAGE

Myocardial Infarction

Metoprolol tartrate injection is indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous metoprolol tartrate can be initiated as soon as the patient's clinical condition allows (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS). Alternatively, treatment can begin within 3 to 10 days of the acute event (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Myocardial Infarction

Metoprolol is contraindicated in patients with a heart rate <45 beats/min; second-and third-degree heart block; significant first-degree heart block (P-R interval ≥0.24 sec); systolic blood pressure <100 mmHg; or moderate-to-severe cardiac failure (see WARNINGS).

WARNINGS

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with metoprolol, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, metoprolol should be discontinued.

Bradycardia: Metoprolol produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to <40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, metoprolol should be discontinued, and cautious administration of isoproterenol or

installation of a cardiac pacemaker should be considered.

AV Block: Metoprolol slows AV conduction and may produce significant first - (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, metoprolol should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤90 mmHg) occurs, metoprolol should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, metoprolol may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, metoprolol should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS

General

Metoprolol should be used with caution in patients with impaired hepatic function.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with metoprolol plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Risk of Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to metoprolol was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when metoprolol is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of metoprolol and placebo described in the CLINICAL PHARMACOLOGY section, the following adverse reactions were reported:

	Metoprolol	Placebo
Hypotension (systolic BP <90 mmHg)	27.4%	23.2%
Bradycardia (heart rate <40 beats min)	15.9%	6.7%
Second-or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158 to 2460; rats, 3090 to 4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see WARNINGS, Myocardial Infarction).

On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., norepinephrine or dopamine.

Bronchospasm: A $beta_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Myocardial Infarction

Early Treatment: During the early phase of definite or suspected acute myocardial infarction, treatment with metoprolol tartrate can be initiated as soon as possible after the patient's arrival in the hospital.

Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of metoprolol tartrate each; the injections should be given at approximately 2-minute intervals. During the intravenous administration of metoprolol tartrate, blood pressure, heart rate, and electrocardiogram should be carefully monitored.

In patients who tolerate the full intravenous dose (15 mg), metoprolol tartrate tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (see *Late Treatment* below).

Patients who appear not to tolerate the full intravenous dose should be started on metoprolol tartrate tablets either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with metoprolol should be discontinued (see WARNINGS).

Late Treatment: Patients with contraindications to treatment during the early phase of suspected or definite myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on metoprolol tartrate tablets, 100 mg twice daily, as soon as their clinical condition allows. Therapy should be continued for at least

3 months. Although the efficacy of metoprolol beyond 3 months has not been conclusively established, data from studies with other beta blockers suggest that treatment should be continued for 1 to 3 years.

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

HOW SUPPLIED

Metoprolol Tartrate Injection, USP is available as:

5 mg/5 mL (1 mg/mL) Ampul, 3 ampuls per carton, List 2285.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not freeze.

PROTECT FROM LIGHT. Retain in carton until time of use.

Discard unused portion.

℞ only

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

5 mL

3 Ampuls -5 mL each

Metoprolol Tartrate Injection, USP
5 mg/5 mL (1 mg per mL)

Each 5 mL contains: 5 mg metoprolol tartrate USP and 45 mg sodium chloride USP in Water for Injection USP.

Usual Dosage: See package insert.

Store at controlled room temperature 15° to 30°C (59° to 86°F)

Do Not Freeze

PROTECT FROM LIGHT. Retain in carton until time of use.
Discard unused portion.

℞ only

RAO5808-2/R1-3/98
Abbott Laboratories, North Chicago, IL 60064, USA
Printed in USA

EXP
LOT

5 mL

Metoprolol Tartrate Injection, USP
5 mg/5 mL (1 mg per mL) **FOR IV USE**

5 mL

3 Ampuls -5 mL each

NDC 0074-2285-05
M-882

Metoprolol Tartrate Injection, USP
5 mg/5 mL (1 mg per mL)
For IV Use

(01) 1 030074 228505 3

5 mL
Metoprolol Tartrate Injection, USP
5 mg/5 mL (1 mg per mL)
FOR IV USE

JUL 6 1998

NDC 0074-2285-05

5 mL

Metoprolol Tartrate Injection, USP

5 mg/5 mL (1 mg per mL)

For IV Use

Store at controlled room temperature 15° to 30°C (59° to 86°F)

PROTECT FROM LIGHT. ℞ only

Abbott Laboratories
North Chicago, IL 60064, USA

RA05807-2/R1-3/98

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75160

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-160

DRUG PRODUCT: Metoprolol Tartrate Injection USP

FIRM: Abbott Hospital Products Division

DOSAGE FORM: Injection

STRENGTH: 1 mg/mL

CGMP STATMENT: Included p. 137

EIR STATUS UPDATE: Overall compliance recommendation acceptable 9/19/97.

BIO STUDY: Waiver request granted 12/31/97

VALIDATION: Not required - USP items

STABILITY: Satisfactory - 24 month expiration

LABELING: Satisfactory - review 4/30/98, A. Vezza & C. Hoppes, HFD-613

STERILIZATION VALIDATION: Satisfactory - review 5/13/98, J. McVey

SIZE OF BIO BATCH: The test batch lot # PD 4-706 is 28L

SIZE OF STABILITY BATCHES: Same as above for the test batch, i.e., 28L

PROPOSED PRODUCTION BATCH: L

/S/ 6/25/98

CHEMIST: Donald Shostak DATE: 3/9/98
(Revised 5/29/98 - micro & label)

TEAM LEADER: Ubrani Venkataram for U.U. /S/ DATE: 6/29/98

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ANDA 75-160

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-160

3. NAME AND ADDRESS OF APPLICANT
Abbott Hospital Products Division
Attention: Thomas Willer, Ph.D.
D-389, Bldg AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537

4. LEGAL BASIS FOR SUBMISSION

The listed drug is Lopressor® Injection (Metoprolol Tartrate, 1 mg/mL) - Geigy Pharmaceuticals.

The applicant states that the patent for Lopressor® Injection is expired and is not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the Act.

5. SUPPLEMENT(s):N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Metoprolol Tartrate Injection USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: June 30, 1997
FAX Amendment: January 30, 1998
Amendment (Labeling): April 17, 1998
Amendment (Micro): May 12, 1998

FDA:
Acknowledgement: July 30, 1997
Micro review # 1: January 16, 1998
C.R. # 1; FAX: January 21, 1998
Micro review # 2: February 10, 1998
Label Review: March 5, 1998
Label review: April 30, 1998
Micro review # 3: May 13, 1998

10. PHARMACOLOGICAL CATEGORY — 11. Rx or OTC
β Adrenoreceptor blocking agent — Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF

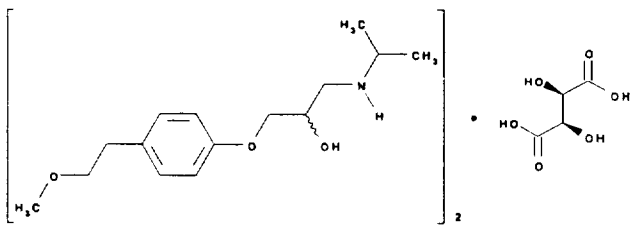
13. DOSAGE FORM
Injection

14. POTENCY
1 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Metoprolol Tartrate USP

$(C_{15}H_{25}NO_3)_2.C_4H_6O_6$; M.W. = 684.82



(±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) (salt). CAS [56392-17-7]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. Chemistry, manufacturing and controls procedures satisfactory.
b. Microbiological review satisfactory 5/8/98
c. Label review satisfactory 4/17/98.
d. EIR satisfactory 9/19/97.
e. Methods validation not required - USP items.
f. Bioequivalence issues are satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

This application can be approved.

19. REVIEWER: Donald Shostak

DATE COMPLETED: March 9, 1998
(Revised 5/29/98, Micro & labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75160

MICROBIOLOGY REVIEW

Mark. A.
1.1

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #1
December 27, 1997

A. 1. ANDA: **75-160**

APPLICANT:
Abbott Laboratories
Hospital Products Division
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
D-0389 AP30 1 East
Abbott Park, IL 60064-3500

2. PRODUCT NAME:
Metoprolol Tartrate Injection USP
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 mg/mL (Ampule)
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Betablocker

B. 1. DATE OF INITIAL SUBMISSION: June 30, 1997.
2. DATE OF AMENDMENT: None.
3. RELATED DOCUMENTS:
4. ASSIGNED FOR REVIEW: December 15, 1997.

C. REMARKS: Reviewed Sterilization volume only. This is product is manufactured at Abbott, McPherson, Kansas.

D. CONCLUSIONS: The submissions are not recommended for approval on the basis of sterility assurance.

/S/ 12/27/97
James L. McVey
initialed by F. Fang or F. Holcombe

1/16/98

cc:
Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey 75160na1.m

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #2
February 9, 1998

A. 1. ANDA: **75-160**

APPLICANT:
Abbott Laboratories
Hospital Products Division
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
D-0389 AP30 1 East
Abbott Park, IL 60064-3500

2. PRODUCT NAME:
Metoprolol Tartrate Injection USP
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 mg/mL (Ampule)
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Betablocker

B. 1. DATE OF INITIAL SUBMISSION: June 30, 1997.
2. DATE OF AMENDMENT: **January 30, 1998 - Subject of this Review.**
3. RELATED DOCUMENTS:
4. ASSIGNED FOR REVIEW: February 9, 1998.

C. REMARKS: This is product is manufactured at Abbott, McPherson, Kansas.

D. CONCLUSIONS: The submissions are not recommended for approval on the basis of sterility assurance.

/S/ 2/9/98
James L. McVey

initialed by F. Fang or F. Holcombe 2/10/98

cc:
Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey 75160na2.m

OFFICE OF GENERIC DRUGS
Microbiologists Review #2
May 13, 1998

A. 1. ANDA: **75-160**

APPLICANT:
Abbott Laboratories
Hospital Products Division
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
D-0389 AP30 1 East
Abbott Park, IL 60064-3500

2. PRODUCT NAME:
Metoprolol Tartrate Injection USP
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 mg/mL (Ampule)
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Betablocker

B. 1. DATE OF INITIAL SUBMISSION: June 30, 1997.
2. DATE OF AMENDMENT: **April 17, 1998 (received April 21, 1998) - Subject of this Review.**
FAX dated May 12, 1998.- Subject of this Review.
3. RELATED DOCUMENTS:
4. ASSIGNED FOR REVIEW: May 8, 1998.

C. REMARKS: This is product is manufactured at Abbott, McPherson, Kansas.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance.

/S/ 5/13/98
James L. McVey

initialed by F. Fang or F. Holcombe 5/15/98

cc:
Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey 75160na2.m

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75160

BIOEQUIVALENCY REVIEW(S)

TLM

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-160 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Metoprolol Tartrate Injection, 1mg/ml, (5ml ampul)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Metoprolol Tartrate Injection	Abbott
1 mg/mL, 5 mL fill Ampul	Abbott Park, IL
ANDA #75-160	Submission Date: 6/30/97
Reviewer: Moo Park	

REF PRODUCT	Geigy's Lopressor[R] Injection, 1 mg/mL
BE STUDY DESIGN	n/a
STUDY RESULTS	n/a
WAIVER	Waiver granted.

INITIAL: /S/ DATE: 12/23/97
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 12/23/97
TEAM LEADER: Ramakant M. Mhatre, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 12/31/97
DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

Metoprolol Tartrate Injection	Abbott
1 mg/mL, 5 mL fill Ampul	Abbott Park, IL
ANDA #75-160	Submission Date: 6/30/97
Reviewer: Moo Park	
Filename: 75160w.697	

Review of a Waiver Request

I. Objective

Review of Abbott's waiver request for its Metoprolol Tartrate Injection, 1 mg/mL. Reference listed product is Geigy's Lopressor^{R} Injection, 1 mg/mL.

II. Comments

1. The test and reference products are injectable solutions. The formulations for the test and reference products are identical. The test and reference formulations are shown in Table 1.

Table 1. Formulation Comparison
Metoprolol Tartrate Injection

Ingredient	Abbott formulation Amount/ampul	Geigy formulation Amount/ampul
Metoprolol Tartrate USP	5 mg	5 mg
Sodium Chloride USP	45 mg	45 mg
Water for Injection USP	qs to 5 mL	qs to 5 mL

2. Waiver is granted.

III. Deficiency

None.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Abbott demonstrates that Metoprolol Tartrate Injection, 1 mg/mL, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Geigy's Lopressor[R] Injection, 1 mg/mL..

The firm should be informed of the recommendation.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ - 12/22/97
Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

/S/

Concur: _____ Date: 12/31/97
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA #75-160 (original, duplicate), Park, Drug File, Division File, HFD-650 (Director)

File history: Draft (9/23/97); Final (12/12/97)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75160

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-160** Date of Submission: **June 30, 1997**

Applicant's Name: **Abbott Laboratories**

Established Name: **Metoprolol Tartrate Injection USP, 1 mg/mL (5 mL Ampule)**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. We acknowledge your commitment to revise the manufacturer's address from Sanofi Winthrop to Abbott throughout your labeling pieces when you submit them in final print.

   b. As a result of the FDA Modernization Act of 1997 please replace the statement with the symbol "Rx only" or "℞ only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CONTAINER 5 mL ampule

   a. See GENERAL COMMENTS.

   b. Store at controlled room temperature 15°-30°C (59°-86°F) - to be the same as the statement in your insert labeling.

3. CARTON

   a. See GENERAL COMMENTS.

   b. BACK PANEL - Revise to read:

      Each 5 mL contains: 5 mg metoprolol tartrate USP and 45 mg sodium chloride USP in Water for Injection USP.

c. See comment 2(b) under CONTAINER.

4. INSERT

a. See GENERAL COMMENTS.

b. "mL" rather than

c. Delete in the following locations:

i. CLINICAL PHARMACOLOGY - everywhere except in the first sentence and the first occurrence in the paragraph beginning "Patients were randomized...".

ii. The CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE sections.

d. Retain "tartrate" throughout the DOSAGE AND ADMINISTRATION section except in the last sentence of the "Early Treatment" subsection and the last sentence of the "Late Treatment" subsection.

e. DESCRIPTION

We encourage the inclusion of the molecular formula.

f. CLINICAL PHARMACOLOGY

i. Italicize "*in vitro*" and "*in vivo*" in the first sentence.

ii. Delete the fifth through the ninth paragraphs (In controlled clinical ... of angina pectoris). This pertains to the oral form of this drug.

iii. Pharmacokinetics

A). Delete the first paragraph and the first sentence of the second paragraph. This pertains to the oral form of this drug.

B). Delete the third sentence of the second paragraph and the third paragraph. This pertains to the oral form of this drug.

C). Paragraph beginning "Following intravenous..." - Delete the hyphens in

the last sentence.

D). Paragraph beginning "Equivalent maximal..." - ... doses ... (plural).

E). Delete the last paragraph ("In patients with ... of the oral dose."). This pertains to the oral form of this drug.

g. PRECAUTIONS

i. "Risk of Anaphylactic Reaction" is a subsection of the PRECAUTIONS section and its title should be in bold print.

ii. Pediatric Use - "pediatric patients" rather than "children".

h. OVERDOSAGE

Hypotension - "norepinephrine" rather than "levarterenol".

Please revise your labels and labeling, as instructed above, and submit final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75160

CORRESPONDENCE

ANDA 75-160

Abbott Hospital Products Division
Attention: Thomas Willer, Ph.D.
200 Abbott Park Road, D-389 AP30
Abbott Park, IL 60064

JUL 30 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Metoprolol Tartrate Injection USP, 1 mg/mL
(5 mL Ampule)

DATE OF APPLICATION: June 30, 1997

DATE OF RECEIPT: July 2, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

7/25/97

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

labeling reviewed 2/13/98 drafted AVS

505(j)(2)(a)(ii) Anna Marie N. Weidel 7/16/97

June 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

Re: Metoprolol Tartrate Injection USP, 1 mg/mL (Ampul)
Original Abbreviated New Drug Application

Dear Mr. Sporn:

Submitted herewith, in duplicate, under § 505(j) of the Federal Food, Drug, and Cosmetic Act, is an original Abbreviated New Drug Application for Metoprolol Tartrate Injection USP, 1 mg/mL, 5 mL fill in 5 mL ampul. In June, 1997, Abbott Laboratories purchased the Sanofi Winthrop Pharmaceuticals manufacturing facility in McPherson, Kansas. This original ANDA applies to that manufacturing facility. In those instances herein where there is a reference to Sanofi, this should be deleted and the reference should be for Abbott Laboratories - McPherson.

Metoprolol Tartrate Injection USP is listed in "Approved Drug Products with Therapeutic Equivalence Evaluations," 17th Edition, page 3-214. A copy appears in Section II.

The active ingredient, indications (applicable to the injection), route of administration, dosage form, and strength for Metoprolol Tartrate Injection USP are the same as those of the innovator's product, Lopressor®, sponsored by Geigy Pharmaceuticals, Division of Ciba-Geigy Corporation. Comparative information is contained in Section IV.

The labeling is the same in content as that of the reference drug, Lopressor®, except for changes that are necessary due to a change in manufacturer. A copy of the innovator's package insert is provided in Section V. Where labeling has Sanofi on it, we will update this to Abbott Laboratories when final printed labeling is submitted.

The first three production batches of Metoprolol Tartrate Injection USP, 1 mg/mL, 5 mL fill in 5 mL, ampul will be placed into our stability program and reported at regular intervals for as long as necessary to support the proposed 24-month expiration date. Our complete stability protocol and post-approval commitments are contained in Section XVII.

For the convenience of the Agency, documentation for Sterilization Process Validation is contained in a separate volume with a dedicated table of contents.

Abbott Laboratories hereby certifies that we have sent a true copy of this letter to and submission to Mr. W. Michael Rogers of the Lenexa, Kansas FDA District Office.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you require any clarification or further information, please call me at (847) 937-6845.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Assistant Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

TFW:tw

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