

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **20491S001**

Trade Name **Corvert Injection 0.1mg/ml**

Generic Name **Ibutilide fumerate**

Sponsor **Pharmacia and Upjohn Company**

Indication Labeling Revision regarding post-cardiac patients

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 20491/S001

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter	X			
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20491/S001

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 13 1999

NDA 20-491/S-001

Pharmacia & Upjohn Company
Attention: Ms. Rebecca K. Tong
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Tong:

Please refer to your supplemental new drug application dated December 19, 1997, received December 22, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Corvert (ibutilide fumarate) Injection, 0.1 mg/ml.

We acknowledge receipt of your submission dated February 25, 1999. Your submission of February 25, 1999 constituted a complete response to our November 19, 1998 action letter.

This supplemental new drug application, as amended, provides for final printed labeling revised to add information to the **CLINICAL PHARMACOLOGY/Clinical Studies**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections regarding post-cardiac surgery patients treated with Corvert.

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 February 25, 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:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,

5/12/99

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20491/S001

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-491/S-001

JUL 2 1998

Pharmacia & Upjohn Company
Attention: Mr. James H. Chambers
7000 Portage Road
Unit 0635-298-113
Kalamazoo, MI 49001

Dear Mr. Chambers:

Please refer to your December 19, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Corvert (ibutilide fumarate) Injection, 0.1 mg/mL.

This supplemental application provides for draft labeling revised to add information to the **CLINICAL PHARMACOLOGY/Clinical Studies, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections regarding post-cardiac surgery patients treated with Corvert.

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

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 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.

NDA 20-491/S-001

Page 2

If you have any questions, contact:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

7/2/98

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

Enclosure

cc:

Archival NDA 20-491

HFD-110/Div. Files

HFD-95/DDMS

DISTRICT OFFICE

HFD-110/D. Willard; 6/24/98 D. Willard 6/24/98

sb/6/24/98; 6/29/98

Initialed by: MGordon/6/25/98

SChen/6/26/98

KSrinivasachar/6/26/98

NMorgenstern/6/25/98

filename: N20491AE.WPD

APPROVABLE (AE)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-491/S-001

NOV 19 1998

Pharmacia & Upjohn Company
Attention: Ms. Robert A. Kreiger
7000 Portage Road
Unit 0635-298-113
Kalamazoo, MI 49001-0199

Dear Ms. Kreiger:

Please refer to your supplemental new drug application dated December 19, 1997, received December 22, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Corvert (ibutilide fumarate) Injection, 0.1 mg/ml.

We acknowledge receipt of your submission dated November 3, 1998.

This supplement provides for draft labeling revised to add information to the **CLINICAL PHARMACOLOGY/Clinical Studies, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections regarding post-cardiac surgery patients treated with Corvert.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the labeling included with your November 3, 1998 submission.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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 314.110. In the absence of any such action FDA may proceed to withdraw the 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:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

11/19/98

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

cc:

Archival NDA 20-491
HFD-110/Div. Files
HFD-002/ORM
HFD-101/ADRA
HFD-95/DDMS
HFD-40/DDMAC (with labeling)
DISTRICT OFFICE
HFD-110/D.Willard;11/17/98
sb/11/16/98;11/20/98
Initialed by: M Gordon/11/17/98
S Chen/11/17/98
N Morgenstern/11/17/98
filename: 20491s001ae.doc

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **20491/S001**

FINAL PRINTED LABELING

Corvert®
ibutilide fumarate injection



For intravenous infusion only

MAY 13 1999

DESCRIPTION

CORVERT Injection (ibutilide fumarate injection) is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification. Each milliliter of CORVERT Injection contains 0.1 mg of ibutilide fumarate (equivalent to 0.087 mg ibutilide free base), 0.189 mg sodium acetate trihydrate, 8.90 mg sodium chloride, hydrochloric acid to adjust pH to approximately 4.6, and Water for Injection.

Corvert
(brand of ibutilide
fumarate injection)

0816418003



Corvert
(brand of ibutilide
fumarate injection)



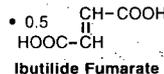
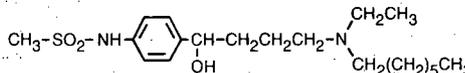
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CORVERT Injection is an isotonic, clear, colorless, sterile aqueous solution. Ibutilide fumarate has one chiral center, and exists as a racemate of the (+) and (-) enantiomers.

The chemical name for ibutilide fumarate is Methanesulfonamide, N-[4-(4-(ethylheptylamino)-1-hydroxybutyl)phenyl], (+) (-), (E)-2-butenedioate (1:0.5) (hemifumarate salt). Its molecular formula is C₂₂H₃₈N₂O₅S, and its molecular weight is 442.62.

Ibutilide fumarate is a white to off-white powder with an aqueous solubility of over 100 mg/mL at pH 7 or lower.

The structural formula is represented below:



CLINICAL PHARMACOLOGY

Mechanism of Action: CORVERT Injection prolongs action potential duration in isolated adult cardiac myocytes and increases both atrial and ventricular refractoriness *in vivo*, ie, class III electrophysiologic effects. Voltage clamp studies indicate that CORVERT, at nanomolar concentrations, delays repolarization by activation of a slow, inward current (predominantly sodium), rather than by blocking outward potassium currents, which is the mechanism by which most other class III antiarrhythmics act. These effects lead to prolongation of atrial and ventricular action potential duration and refractoriness, the predominant electrophysiologic properties of CORVERT in humans that are thought to be the basis for its antiarrhythmic effect.

Electrophysiologic Effects: CORVERT produces mild slowing of the sinus rate and atrioventricular conduction. CORVERT produces no clinically significant effect on QRS duration at intravenous doses up to 0.03 mg/kg administered over a 10-minute period. Although there is no established relationship between plasma concentration and antiarrhythmic effect, CORVERT produces dose-related prolongation of the QT interval, which is thought to be associated with its antiarrhythmic activity. (See WARNINGS for relationship between QTc prolongation and torsades de pointes-type arrhythmias.) In a study in healthy volunteers, intravenous infusions of CORVERT resulted in prolongation of the QT interval that was directly correlated with ibutilide plasma concentration during and after 10-minute and 8-hour infusions. A steep ibutilide concentration/response (QT prolongation) relationship was shown. The maximum effect was a function of both the dose of CORVERT and the infusion rate.

Hemodynamic Effects: A study of hemodynamic function in patients with ejection fractions both above and below 35% showed no clinically significant effects on cardiac output, mean pulmonary arterial pressure, or pulmonary capillary wedge pressure at doses of CORVERT

up to 0.03 mg/kg.

Pharmacokinetics: After intravenous infusion, ibutilide plasma concentrations rapidly decrease in a multiexponential fashion. The pharmacokinetics of ibutilide are highly variable among subjects. Ibutilide has a high systemic plasma clearance that approximates liver blood flow (about 29 mL/min/kg), a large steady-state volume of distribution (about 11 L/kg) in healthy volunteers, and minimal (about 40%) protein binding. Ibutilide is also cleared rapidly and highly distributed in patients being treated for atrial flutter or atrial fibrillation. The elimination half-life averages about 6 hours (range from 2 to 12 hours). The pharmacokinetics of ibutilide are linear with respect to the dose of CORVERT over the dose range of 0.01 mg/kg to 0.10 mg/kg. The enantiomers of ibutilide fumarate have pharmacokinetic properties similar to each other and to ibutilide fumarate.

The pharmacokinetics of CORVERT injection in patients with atrial flutter or atrial fibrillation are similar regardless of the type of arrhythmia, patient age, sex, or the concomitant use of digoxin, calcium channel blockers, or beta blockers.

Metabolism and elimination: In healthy male volunteers, about 82% of a 0.01 mg/kg dose of [¹⁴C] ibutilide fumarate was excreted in the urine (about 7% of the dose as unchanged ibutilide) and the remainder (about 19%) was recovered in the feces.

Eight metabolites of ibutilide were detected in metabolic profiling of urine. These metabolites are thought to be formed primarily by ω -oxidation followed by sequential β -oxidation of the heptyl side chain of ibutilide. Of the eight metabolites, only the ω -hydroxy metabolite possesses class III electrophysiologic properties similar to that of ibutilide in an *in vitro* isolated rabbit myocardium model. The plasma concentrations of this active metabolite, however, are less than 10% of that of ibutilide.

Clinical Studies: Treatment with intravenous ibutilide fumarate for acute termination of recent onset atrial flutter/fibrillation was evaluated in 466 patients participating in two randomized, double-blind, placebo-controlled clinical trials. Patients had had their arrhythmias for 3 hours to 90 days, were anticoagulated for at least 2 weeks if atrial fibrillation was present more than 3 days, had serum potassium of at least 4.0 mEq/L and QTc below 440 msec, and were monitored by telemetry for at least 24 hours. Patients could not be on class I or other class III antiarrhythmics (these had to be discontinued at least 5 half-lives prior to infusion) but could be on calcium channel blockers, beta blockers, or digoxin. In one trial, single 10-minute infusions of 0.005 to 0.025 mg/kg were tested in parallel groups (0.3 to 1.5 mg in a 60 kg person). In the second trial, up to two infusions of ibutilide fumarate were evaluated—the first 1.0 mg, the second given 10 minutes after completion of the first infusion, either 0.5 or 1.0 mg. In a third double-blind study, 319 patients with atrial fibrillation or atrial flutter of 3 hours to 45 days duration were randomized to receive single, 10-minute intravenous infusions of either sotalolol (1.5 mg/kg) or CORVERT (1 mg or 2 mg). Among patients with atrial flutter, 53% receiving 1 mg ibutilide fumarate and 70% receiving 2 mg ibutilide fumarate converted, compared to 18% of those receiving sotalolol. In patients with atrial fibrillation, 22% receiving 1 mg ibutilide fumarate and 43% receiving 2 mg ibutilide fumarate converted compared to 10% of patients receiving sotalolol.

Patients in registration trials were hemodynamically stable. Patients with specific cardiovascular conditions such as symptomatic heart failure, recent acute myocardial infarction, and angina were excluded. About two thirds had cardiovascular symptoms, and the majority of patients had left atrial enlargement, decreased left ventricular ejection fraction, a history of valvular disease, or previous history of atrial fibrillation or flutter. Electrical cardioversion was allowed 90 minutes after the infusion was complete. Patients could be given other antiarrhythmic drugs 4 hours postinfusion.

Results of the first two studies are shown in the tables below. Conversion of atrial flutter/fibrillation usually (70% of those who converted) occurred within 30 minutes of the start of infusion and was dose related. The latest conversion seen was at 90 minutes after the start of the infusion. Most converted patients remained in normal sinus rhythm for 24 hours. Overall responses in these patients, defined as termination of arrhythmias for any length of time during or within 1 hour following completed infusion of randomized dose, were in the range of 43% to 48% at doses above 0.0125 mg/kg (vs 2% for placebo). Twenty-four hour responses were similar. For these atrial arrhythmias, ibutilide was more effective in patients with flutter than fibrillation ($\geq 48\%$ vs $\leq 40\%$).

PERCENT OF PATIENTS WHO CONVERTED (First Trial)						
		Ibutilide				
		Placebo	0.005 mg/kg	0.01 mg/kg	0.015 mg/kg	0.025 mg/kg
	n	41	41	40	38	40
Both	Initially*	2	12	33	45	48
	At 24 hours†	2	12	28	42	43
Atrial flutter	Initially*	0	14	30	58	55
	At 24 hours†	0	14	30	58	50
Atrial fibrillation	Initially*	5	10	35	32	40
	At 24 hours†	5	10	25	26	35

* Percent of patients who converted within 70 minutes after the start of infusion.

† Percent of patients who remained in sinus rhythm 24 hours after dosing.

PERCENT OF PATIENTS WHO CONVERTED (Second Trial)				
		Ibutilide		
		Placebo	1.0 mg/0.5 mg	1.0 mg/1.0 mg
	n	86	86	94
Both	Initially*	2	43	44
	At 24 hours†	2	34	37
Atrial flutter	Initially*	2	48	63
	At 24 hours†	2	45	59
Atrial fibrillation	Initially*	2	38	25
	At 24 hours†	2	21	17

* Percent of patients who converted within 90 minutes after the start of infusion.

† Percent of patients who remained in sinus rhythm 24 hours after dosing.

The numbers of patients who remained in the converted rhythm at the end of 24 hours were slightly less than those patients who converted initially, but the difference between conversion rates for ibutilide compared to placebo was still statistically significant. In long-term follow-up, approximately 40% of all patients remained recurrence free, usually with chronic prophylactic treatment, 400 to 500 days after acute treatment, regardless of the method of conversion.

Patients with more recent onset of arrhythmia had a higher rate of conversion. Response rates were 42% and 50% for patients with onset of atrial fibrillation/flutter for less than 30 days in the two efficacy studies compared to 16% and 31% in those with more chronic arrhythmias.

Ibutilide was equally effective in patients below and above 65 years of age and in men and women. Female patients constituted about 20% of patients in controlled studies.

Post-cardiac Surgery: In a double-blind, parallel group study, 302 patients with atrial fibrillation (n=201) or atrial flutter (n=101) that occurred 1 to 7 days after coronary artery bypass graft or valvular surgery and lasted 1 hour to 3 days were randomized to receive two 10-minute infusions of placebo, or 0.25, 0.5 or 1 mg of ibutilide fumarate. Among patients with atrial flutter, conversion rates at 1.5 hours were: placebo, 4%; 0.25 mg ibutilide fumarate, 56%; 0.5 mg ibutilide fumarate, 61%; and 1 mg ibutilide fumarate, 78%. Among patients with atrial fibrillation, conversion rates at 1.5 hours were: placebo, 20%; 0.25 mg ibutilide fumarate, 28%; 0.5 mg ibutilide fumarate, 42%, and 1 mg ibutilide fumarate, 44%. The majority of patients (53% and 72% in the 0.5-mg and 1-mg dose groups, respectively) converted to sinus rhythm remained in sinus rhythm for 24 hours. Patients were not given other antiarrhythmic drugs within 24 hours of ibutilide fumarate infusion in this study.

INDICATIONS AND USAGE

CORVERT Injection is indicated for the rapid conversion of atrial fibrillation or atrial flutter of recent onset to sinus rhythm. Patients with atrial arrhythmias of longer duration are less likely to respond to CORVERT. The effectiveness of ibutilide has not been determined in patients with arrhythmias of more than 90 days in duration.

LIFE-THREATENING ARRHYTHMIAS—APPROPRIATE TREATMENT ENVIRONMENT

CORVERT can cause potentially fatal arrhythmias, particularly sustained polymorphic ventricular tachycardia, usually in association with QT prolongation (torsades de pointes), but sometimes without documented QT prolongation. In registration studies, these arrhythmias, which require cardioversion, occurred in 1.7% of treated patients during, or within a number of hours of, use of CORVERT. These arrhythmias can be reversed if treated promptly (see WARNINGS, Proarrhythmia). It is essential that CORVERT be administered in a setting of continuous ECG monitoring and by personnel trained in identification and treatment of acute ventricular arrhythmias, particularly polymorphic ventricular tachycardia. Patients with atrial fibrillation of more than 2 to 3 days' duration must be adequately anticoagulated, generally for at least 2 weeks.

CHOICE OF PATIENTS

Patients with chronic atrial fibrillation have a strong tendency to revert after conversion to sinus rhythm (see CLINICAL STUDIES) and treatments to maintain sinus rhythm carry risks. Patients to be treated with CORVERT, therefore, should be carefully selected such that the expected benefits of maintaining sinus rhythm outweigh the immediate risks of CORVERT, and the risks of maintenance therapy, and are likely to offer an advantage compared with alternative management.

CONTRAINDICATIONS

CORVERT Injection is contraindicated in patients who have previously demonstrated hypersensitivity to ibutilide fumarate or any of the other product components.

WARNINGS

Proarrhythmia: Like other antiarrhythmic agents, CORVERT Injection can induce or worsen ventricular arrhythmias in some patients. This may have potentially fatal consequences. Torsades de pointes, a polymorphic ventricular tachycardia that develops in the setting of a prolonged QT interval, may occur because of the effect CORVERT has on cardiac repolarization, but CORVERT can also cause polymorphic VT in the absence of excessive prolongation of the QT interval. In general, with drugs that prolong the QT interval, the risk of torsades de pointes is thought to increase progressively as the QT interval is prolonged and may be worsened with bradycardia, a varying heart rate, and hypokalemia. In clinical trials conducted in patients with atrial fibrillation and atrial flutter, those with QTc intervals >440 msec were not usually allowed to participate, and serum potassium had to be above 4.0 mEq/L. Although change in QTc was dose dependent for ibutilide, there was no clear rela-

Corvert®

brand of ibutilide fumarate injection

relationship between risk of serious proarrhythmia and dose in clinical studies, possibly due to the small number of events. In clinical trials of intravenous ibutilide, patients with a history of congestive heart failure (CHF) or low left ventricular ejection fraction appeared to have a higher incidence of sustained polymorphic ventricular tachycardia (VT), than those without such underlying conditions; for sustained polymorphic VT the rate was 5.4% in patients with a history of CHF and 0.8% without it. There was also a suggestion that women had a higher risk of proarrhythmia, but the sex difference was not observed in all studies and was most prominent for nonsustained ventricular tachycardia. The incidence of sustained ventricular arrhythmias was similar in male (1.8%) and female (1.5%) patients, possibly due to the small number of events. CORVERT is not recommended in patients who have previously demonstrated polymorphic ventricular tachycardia (eg, torsades de pointes).

(continued below)

During registration trials, 1.7% of patients with atrial flutter or atrial fibrillation treated with CORVERT developed sustained polymorphic ventricular tachycardia requiring cardioversion. In these clinical trials, many initial episodes of polymorphic ventricular tachycardia occurred after the infusion of CORVERT was stopped but generally not more than 40 minutes after the start of the first infusion. There were, however, instances of recurrent polymorphic VT that occurred about 3 hours after the initial infusion. In two cases, the VT degenerated into ventricular fibrillation, requiring immediate defibrillation. Other cases were managed with cardiac pacing and magnesium sulfate infusions. Nonsustained polymorphic ventricular tachycardia occurred in 2.7% of patients and nonsustained monomorphic ventricular tachycardias occurred in 4.9% of the patients (see ADVERSE REACTIONS).

Proarrhythmic events must be anticipated. Skilled personnel and proper equipment, including cardiac monitoring equipment, intracardiac pacing facilities, a cardioverter/defibrillator, and medication for treatment of sustained ventricular tachycardia, including polymorphic ventricular tachycardia, must be available during and after administration of CORVERT. Before treatment with CORVERT, hypokalemia and hypomagnesemia should be corrected to reduce the potential for proarrhythmia. Patients should be observed with continuous ECG monitoring for at least 4 hours following infusion or until QTc has returned to baseline. Longer monitoring is required if any arrhythmic activity is noted. Management of polymorphic ventricular tachycardia includes discontinuation of ibutilide, correction of electrolyte abnormalities, especially potassium and magnesium, and override cardiac pacing, electrical cardioversion, or defibrillation. Pharmacologic therapies include magnesium sulfate infusions. Treatment with antiarrhythmics should generally be avoided.

PRECAUTIONS

General

Antiarrhythmics: Class Ia antiarrhythmic drugs (Vaughan Williams Classification), such as disopyramide, quinidine, and procainamide, and other class III drugs, such as amiodarone and sotalol, should not be given concomitantly with CORVERT Injection or within 4 hours postinfusion because of their potential to prolong refractoriness. In the clinical trials, class I or other class III antiarrhythmic agents were withheld for at least 5 half-lives prior to ibutilide infusion and for 4 hours after dosing, but thereafter were allowed at the physician's discretion.

Other drugs that prolong the QT Interval: The potential for proarrhythmia may increase with the administration of CORVERT Injection to patients who are being treated with drugs that prolong the QT interval, such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, and certain antihistamine drugs (H₁ receptor antagonists).

Heart block: Of the nine (1.5%) ibutilide-treated patients with reports of reversible heart block, five had first degree, three had second degree, and one had complete heart block.

Laboratory Test Interactions: None known.

Drug Interactions: No specific pharmacokinetic or other formal drug interaction studies were conducted.

Digoxin: Supraventricular arrhythmias may mask the cardiotoxicity associated with excessive digoxin levels. Therefore, it is advisable to be particularly cautious in patients whose plasma digoxin levels are above or suspected to be above the usual therapeutic range. Coadministration of digoxin did not have effects on either the safety or efficacy of ibutilide in the clinical trials.

Calcium channel blocking agents: Coadministration of calcium channel blockers did not have any effect on either the safety or efficacy of ibutilide in the clinical trials.

Beta-adrenergic blocking agents: Coadministration of beta-adrenergic blocking agents did not have any effect on either the safety or efficacy of ibutilide in the clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal studies have been conducted to determine the carcinogenic potential of CORVERT; however, it was not genotoxic in a battery of assays, (Ames assay, mammalian cell forward gene mutation assay, unscheduled DNA synthesis assay, and mouse micronucleus assay). Similarly, no drug-related effects on fertility or mating were noted in a reproductive study in rats in which ibutilide was administered orally to both sexes up to doses of 20 mg/kg/day. On a mg/m² basis, corrected for 3% bioavailability, the highest dose tested was approximately four times the maximum recommended human dose (MRHD).

Pregnancy: Pregnancy Category C. Ibutilide administered orally was teratogenic (abnormalities included adactyly, interventricular septal defects, and scoliosis) and embryocidal in reproduction studies in rats. On a mg/m² basis, corrected for the 3% oral bioavailability, the "no adverse effect dose" (5 mg/kg/day given orally) was approximately the same as the maximum recommended human dose (MRHD); the teratogenic dose (20 mg/kg/day given orally) was about four times the MRHD on a mg/m² basis, or 16 times the MRHD on a mg/kg basis. CORVERT should not be administered to a pregnant woman unless clinical benefit outweighs potential risk to the fetus.

Nursing Mothers: The excretion of ibutilide into breast milk has not been studied; accordingly, breastfeeding should be discouraged during therapy with CORVERT.

Pediatric Use: Clinical trials with CORVERT in patients with atrial fibrillation and atrial flutter did not include anyone under the age of 18. Safety and effectiveness of ibutilide in pediatric patients has not been established.

Geriatric Use: The mean age of patients in clinical trials was 65. No age-related differences were observed in pharmacokinetic, efficacy, or safety parameters for patients less than 65 compared to patients 65 years and older.

Use in Patients With Hepatic or Renal Dysfunction: The safety, effectiveness, and pharmacokinetics of CORVERT have not been established in patients with hepatic or renal dysfunction. However, it is unlikely that dosing adjustments would be necessary in patients with compromised renal or hepatic function based on the following considerations: (1) CORVERT is indicated for rapid intravenous therapy (duration \leq 30 minutes) and is dosed to a known, well-defined pharmacologic action (termination of arrhythmia) or to a maximum of two 10-minute infusions; (2) less than 10% of the dose of CORVERT is excreted unchanged in the urine; and (3) drug distribution appears to be one of the primary mechanisms responsible for termination of the pharmacologic effect. Nonetheless, patients with abnormal liver function should be monitored by telemetry for more than the 4-hour period generally recommended.

In 285 patients with atrial fibrillation or atrial flutter who were treated with CORVERT, the clearance of ibutilide was independent of renal function, as assessed by creatinine clearance (range 21 to 140 mL/min).

ADVERSE REACTIONS

CORVERT Injection was generally well tolerated in clinical trials. Of the 586 patients with atrial fibrillation or atrial flutter who received CORVERT in phase I/III studies, 149 (25%) reported medical events related to the cardiovascular system, including sustained polymorphic ventricular tachycardia (1.7%) and nonsustained polymorphic ventricular tachycardia (2.7%).

Other clinically important adverse events with an uncertain relationship to CORVERT include the following (0.2% represents one patient): sustained monomorphic ventricular tachycardia (0.2%), nonsustained monomorphic ventricular tachycardia (4.9%), AV block (1.5%), bundle branch block (1.9%), ventricular extrasystoles (5.1%), supraventricular extrasystoles (0.9%), hypotension/postural hypotension (2.0%), bradycardia/sinus bradycardia (1.2%), nodal arrhythmia (0.7%), congestive heart failure (0.5%), tachycardia/sinus tachycardia/supraventricular tachycardia (2.7%), idioventricular rhythm (0.2%), syncope (0.3%), and renal failure (0.3%). The incidence of these events, except for syncope, was greater in the group treated with CORVERT than in the placebo group.

Another adverse reaction that may be associated with the administration of CORVERT was nausea, which occurred with a frequency greater than 1% more in ibutilide-treated patients than those treated with placebo.

The medical events reported for more than 1% of the placebo- and ibutilide-treated patients are shown in the following Table.

Treatment-Emergent Medical Events With Frequency of More Than 1% and Higher Than That of Placebo

Event	Placebo N=127		All Ibutilide N=586	
	Patients		Patients	
	n	%	n	%
CARDIOVASCULAR				
Ventricular extrasystoles	1	0.8	30	5.1
Nonsustained monomorphic VT	1	0.8	29	4.9
Nonsustained polymorphic VT	—	—	16	2.7
Hypotension	2	1.6	12	2.0
Bundle branch block	—	—	11	1.9
Sustained polymorphic VT	—	—	10	1.7
AV block	1	0.8	9	1.5
Hypertension	—	—	7	1.2
QT segment prolonged	—	—	7	1.2

PERCENT OF PATIENTS WHO CONVERTED (Second Trial)				
		Ibutilide		
		Placebo	1.0 mg/0.5 mg	1.0 mg/1.0 mg
	n	86	86	94
Both	Initially*	2	43	44
	At 24 hours†	2	34	37
Atrial flutter	Initially*	2	48	63
	At 24 hours†	2	45	59
Atrial fibrillation	Initially*	2	38	25
	At 24 hours†	2	21	17

* Percent of patients who converted within 90 minutes after the start of infusion.

† Percent of patients who remained in sinus rhythm 24 hours after dosing.

The numbers of patients who remained in the converted rhythm at the end of 24 hours were slightly less than those patients who converted initially, but the difference between conversion rates for ibutilide compared to placebo was still statistically significant. In long-term follow-up, approximately 40% of all patients remained recurrence free, usually with chronic prophylactic treatment, 400 to 500 days after acute treatment, regardless of the method of conversion.

Patients with more recent onset of arrhythmia had a higher rate of conversion. Response rates were 42% and 50% for patients with onset of atrial fibrillation/flutter for less than 30 days in the two efficacy studies compared to 16% and 31% in those with more chronic arrhythmias.

Ibutilide was equally effective in patients below and above 65 years of age and in men and women. Female patients constituted about 20% of patients in controlled studies.

Post-cardiac Surgery: In a double-blind, parallel group study, 302 patients with atrial fibrillation (n=201) or atrial flutter (n=101) that occurred 1 to 7 days after coronary artery bypass graft or valvular surgery and lasted 1 hour to 3 days were randomized to receive two 10-minute infusions of placebo, or 0.25, 0.5 or 1 mg of ibutilide fumarate. Among patients with atrial flutter, conversion rates at 1.5 hours were: placebo, 4%; 0.25 mg ibutilide fumarate, 56%; 0.5 mg ibutilide fumarate, 61%; and 1 mg ibutilide fumarate, 78%. Among patients with atrial fibrillation, conversion rates at 1.5 hours were: placebo, 20%; 0.25 mg ibutilide fumarate, 28%; 0.5 mg ibutilide fumarate, 42%, and 1 mg ibutilide fumarate, 44%. The majority of patients (53% and 72% in the 0.5-mg and 1-mg dose groups, respectively) converted to sinus rhythm remained in sinus rhythm for 24 hours. Patients were not given other antiarrhythmic drugs within 24 hours of ibutilide fumarate infusion in this study.

INDICATIONS AND USAGE

CORVERT Injection is indicated for the rapid conversion of atrial fibrillation or atrial flutter of recent onset to sinus rhythm. Patients with atrial arrhythmias of longer duration are less likely to respond to CORVERT. The effectiveness of ibutilide has not been determined in patients with arrhythmias of more than 90 days in duration.

LIFE-THREATENING ARRHYTHMIAS—APPROPRIATE TREATMENT ENVIRONMENT

CORVERT can cause potentially fatal arrhythmias, particularly sustained polymorphic ventricular tachycardia, usually in association with QT prolongation (torsades de pointes), but sometimes without documented QT prolongation. In registration studies, these arrhythmias, which require cardioversion, occurred in 1.7% of treated patients during, or within a number of hours of, use of CORVERT. These arrhythmias can be reversed if treated promptly (see WARNINGS, Proarrhythmia). It is essential that CORVERT be administered in a setting of continuous ECG monitoring and by personnel trained in identification and treatment of acute ventricular arrhythmias, particularly polymorphic ventricular tachycardia. *Patients with atrial fibrillation of more than 2 to 3 days' duration must be adequately anticoagulated, generally for at least 2 weeks.*

CHOICE OF PATIENTS

Patients with chronic atrial fibrillation have a strong tendency to revert after conversion to sinus rhythm (see CLINICAL STUDIES) and treatments to maintain sinus rhythm carry risks. Patients to be treated with CORVERT, therefore, should be carefully selected such that the expected benefits of maintaining sinus rhythm outweigh the immediate risks of CORVERT, and the risks of maintenance therapy, and are likely to offer an advantage compared with alternative management.

CONTRAINDICATIONS

CORVERT Injection is contraindicated in patients who have previously demonstrated hypersensitivity to ibutilide fumarate or any of the other product components.

WARNINGS

Proarrhythmia: Like other antiarrhythmic agents, CORVERT Injection can induce or worsen ventricular arrhythmias in some patients. This may have potentially fatal consequences. Torsades de pointes, a polymorphic ventricular tachycardia that develops in the setting of a prolonged QT interval, may occur because of the effect CORVERT has on cardiac repolarization, but CORVERT can also cause polymorphic VT in the absence of excessive prolongation of the QT interval. In general, with drugs that prolong the QT interval, the risk of torsades de pointes is thought to increase progressively as the QT interval is prolonged and may be worsened with bradycardia, a varying heart rate, and hypokalemia. In clinical trials conducted in patients with atrial fibrillation and atrial flutter, those with QTc intervals >440 msec were not usually allowed to participate, and serum potassium had to be above 4.0 mEq/L. Although change in QTc was dose dependent for ibutilide, there was no clear rela-

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20491/S001

MEDICAL REVIEW(S)

APR 2 1998

DIVISION OF CARDIO RENAL DRUG PRODUCTS
MEDICAL REVIEW OF INFORMATION AMENDMENT

NDA # 20,491 dated Dec. 19, 1997

Sponsor: Pharmacia and Upjohn

Drug name: ibutilide

Medical reviewer: Maryann Gordon M

Through: Shaw Chen, MD, PhD

Submission: 7 volumes including ~~study report, data tables, and appendices~~; no case report forms for any of the study patients were provided. 3-23-98
~~3-23-98~~

Introduction

Ibutilide fumarate, an intravenous class III antiarrhythmic agent, was approved in 1995 for the acute conversion of atrial fibrillation/atrial flutter.

Protocol M/7550/0017

Entitled "A study of the conversion efficacy and safety of repeated intravenous doses of ibutilide in patients with atrial flutter or atrial fibrillation following valvular or coronary artery bypass surgery." The protocol is dated January 7, 1993.

The main study objective was to demonstrate the effectiveness of ibutilide compared to placebo in the termination of atrial arrhythmia (atrial flutter (afl) or atrial fibrillation (afib)) that developed in patients who had recently undergone cardiac surgery. Other study objectives included examining the effect of a second dose of ibutilide on the rate of termination and the overall safety of ibutilide in this patient population.

The study design was double blind, randomized, placebo controlled, with parallel treatment arms. The doses of ibutilide were 0.25, 0.5, or 1 mg (0.0025, 0.005, or 0.01 mg/kg in patients weighing less than 60 kg). The study drug was infused for 10 minutes. This was followed by a 10 minute wait and another 10 minute infusion in those patients who had not converted and had not experienced a serious arrhythmia. Treatment success was defined as termination of the index arrhythmia for any length of time but prior to hour 1.5. At hour 24, all patients (i.e., both successes and failures) were evaluated for heart rhythm and whether additional treatment, if any, was given subsequent to hour 1.5. The use of additional antiarrhythmics in successes was to be delayed until hour 24. The use of additional antiarrhythmics in failures was to be delayed until hour 4. Failures could have been paced or DC cardioverted after hour 1.5. At hour 72, all patients were queried about adverse events

A total of 300 study patients (75 patients per group for each of the 4 treatment groups) were planned. Patients had to have a rhythm of sustained afl or afib (duration > 3 hours but < 3 days) that occurred between 24 hours and 7 days after CABG. Patients could not have a history of afl or afib prior to surgery (this was later amended), a history of torsades de pointes (tdp), or prior exposure to ibutilide. The QTc interval at baseline had to be no greater than 440 msec on 12-lead ECG and patients had to be hemodynamically stable with blood pressure >90/<105 mm Hg and without symptoms of unstable angina or CHF. The lower age and upper weight limits were 18 years and 300 lbs, respectively. Females had to be either surgically sterile or postmenopausal. Patients could not have had a myocardial infarct

within 30 days of study. Patients could not have evidence of hyperthyroidism or other serious disease, or have had cardiac surgery other than CABG. Patients with liver enzymes more than 2 times upper limit of normal were excluded as were patients on class I or class III antiarrhythmics (unless the drugs had been discontinued for more than 5 half lives previously) and those thought to have toxic levels of digoxin. Patients also had to have their doses of epinephrine, amrinone, dopamine or dobutamine if they were taking such drugs.

The primary endpoint was the termination of the index arrhythmia prior to hour 1.5 and without interventions other than study drug. There were no restrictions on the type or the duration of the resulting rhythm in classifying a patient as a "success."

Amendment (dated August 9, 1993)

- expanded patient population to include patients who underwent valvular surgery,
- decreased duration of sustained afl or afib from 3 to 1 hour,
- removed the exclusion of patients with history of pre-op afl or afib.

Results

Demographics

There were 302 patients enrolled into the study: 101 with afl and 201 with afib. The majority of patients (208) had undergone CABG, 60 patients had undergone valvular surgery, and 34 had undergone both procedures. Eight patients had a previous history of afl/afib (letter from sponsor dated 3-23-98).

Twenty-nine centers, all in the US, enrolled patients. Nine of the centers enrolled less than 3 patients. A total of 76 patients were randomized but did not receive study drug because their arrhythmia had spontaneously terminated prior to first infusion.

For all patients, the mean age was 68.5 years, 97% were white, and 24% were female. Of the patients who had ejection fractions recorded at baseline, 31% had impaired cardiac function (table G.1).

Number of randomized patients

total	placebo	ibutilide dose (mg)		
		0.25	0.5	1.0
afl	24	32	18	27
afib	<u>60</u>	<u>43</u>	<u>55</u>	<u>43</u>
total	84	75	73	70

There were no significant differences among treatments groups (combining afl and afib) for age, height, weight, sex or race (Tables F.1-5).

The mean duration of the index arrhythmia was 1.03 days for all 301 study patients (minimum and maximum durations were 0.03 and 3.50 days, respectively). The mean duration for the placebo,

ibutilide 0.25 mg, 0.5 mg, and 1.0 mg groups were 1.06, 0.97, 1.02, and 1.05 days, respectively.

Disposition of patients

Of the 302 patients enrolled, 5 (2%) were discontinued prematurely: 1 patient per treatment group except for the 1 mg group which had 2 discontinues. Patient #3193 (ibutilide 0.25 mg) was withdrawn prior to receiving study drug when it was discovered that propafenone had been recently administered. All patients with the exception of #3193 were included in the efficacy analyses.

There were numerous dosing and administration errors, usually because the dose was not recalculated for weights under 60 kg. Patient #3236 received 1 mg ibutilide rather than 0.5 mg to which he was randomized; he was analyzed with the 1 mg group.

Termination of arrhythmia

The primary endpoint was defined as arrhythmia termination, for any length of time, by hour 1.5 after start of infusion and without interventions other than study drug. The number of patients who were successes, by treatment group and index arrhythmia, are shown below.

Number and (percent) of patients

	ibutilide mg			
	placebo	0.25	0.5	1.0
afl	1/24 (4)	18/32 (56)	11/18 (61)	21/27 (78)
afib	12/60 (20)	12/43 (28)	23/55 (42)	19/43 (44)
total	13/84 (15)	30/75 (40)	34/73 (47)	40/70 (57)

table K.1

The number of successes in the ibutilide group were >2 - 3 fold greater than the placebo successes, and there was a dose response. Ibutilide, at all doses, was more successful in converting afl than afib.

The table below shows the p-values for placebo vs. ibutilide by dose group and by arrhythmia.

P-values

	ibutilide mg		
	0.25	0.5	1.0
afl	<0.0001	0.0001	<0.0001
afib	ns	0.01	0.008
total	0.0005	<0.0001	<0.0001

table K.1A

Ibutilide 0.5 and 1.0 mg doses in this study were highly effective, compared to placebo, in terminating afl, especially, and afib in the study patients. Although ibutilide 0.25 mg was not significantly different from placebo in terminating afib ($p=0.349$), it was highly effective in terminating afl.

The table below shows the patients, by dose group, who converted either during or within 10 minutes of receiving the first infusion of study drug.

Number and (percent) of patients converting with 1 infusion

	ibutilide mg			
	placebo n=13+	0.25 n=30+	0.5 n=34+	1.0 n=40+
afl	0	5	7	16
afib	1	4	6	10
total	1 (8)	9 (30)	13 (38)	26 (65)

+total number of successes

table K.2

The higher the dose of ibutilide, the more likely patients needed only 1 infusion in order to convert.

Of the 61% of patients who were study failures, most had their arrhythmia terminated between hours 1.5 and 24 by DC cardioversion, other medications, pacing, or they had spontaneous conversions. The remaining patients either had no attempt made to convert them or the attempt failed.

Number of patients

	ibutilide			
	placebo n=71+	0.25 n=45+	0.5 n=39+	1.0 n=29+^
DC cardioversion	11	2	4	6
medication	15	6	5	2
pacing	0	1	2	0
spontaneous	14	12	16	7
no attempt made	17	12	9	9
failed attempt	14	12	3	5

+total number of failures

^1 patient was paced prior to hour 1.5 and excluded.

Tables K.10 and K.11

The table below shows the number of study drug successes who remained in the converted rhythm through hour 24.

Number and (percent) of patients

	ibutilide			
	placebo n=13+	0.25 n=29+^	0.5 n=34+	1.0 n=39+^
remained converted through hour 24	8 (62)	19 (66)	18 (53)	28 (72)

+number of successes

^missing 1 patient

Table K.14

The majority of successes remained converted at least through hour 24. However, 6 of these had received a concomitant antiarrhythmic medication prior to hour 24: 1 placebo (sotalol), 2-0.25mg (rythmol, procainamide), 2-0.5 mg (rythmol, procainamide), and 1-1mg (procan SR). As stated previously, 8 of the patients (2 placebo, 6 ibutilide) had a history of afl/afib. Of the 6 patients randomized to ibutilide, it is surprising that only 2 converted and remained in sinus rhythm at 24 hours (letter from sponsor dated 3-23-98).

The table below shows the number of successes who converted to sinus rhythm and those who converted to an alternate rhythm.

Number of patients

	ibutilide			
	placebo n=13+	0.25 n=30+	0.5 n=34+	1.0 n=40+
normal sinus rhythm	6	19	18	28
alternate rhythm	7	11	16	12

+number of successes

Table K.15

The majority of successes had converted to normal sinus rhythm.

The mean durations of index arrhythmia for success and failure, by treatment group and type of arrhythmia, are shown below.

Mean duration of index arrhythmia (days)

dose (all successes/all failures)	successes	failures
all placebo (13/71)	0.55	1.16
placebo afl (1/23)	2.01	1.21
placebo afib (12/48)	0.42	1.13
all ibutilide 0.25 mg (30/44)	0.89	1.03
0.25 mg afl (18/13)	0.76	1.5
0.25 mg afib (12/31)	1.08	0.84
all ibutilide 0.5 mg (34/39)	0.89	1.14
0.5 mg afl (11/7)	0.68	1.51
0.5 mg afib (23/32)	0.99	1.05
all ibutilide 1.0 mg (40/30)	1.03	1.09
1.0 mg afl (21/6)	1.07	1.66
1.0 mg afib (19/24)	0.98	0.95

tables K.22 and K.23

Except in a few isolated cases, the successes tended to have spent less time in their index arrhythmia than the failures.

Concomitant medications

The 5 most common medications taken by patients prior to receiving study drug were digoxin (87%), aspirin (67%), acetaminophen (62%), potassium (60%), and furosemide (59%) (table O.1). The 5 most common medications taken by patients between the end of the infusion of study drug and hour 24 were digoxin (19%), procainamide (19%), acetaminophen (13%), potassium (13%), and furosemide (12%) (table O.2).

Safety

Adverse events

The number and percent of patients who reported at least one adverse event, by body system and treatment group, are shown below.

Number and (percent) of patients

reported adverse event	placebo n=84	ibutilide		
		0.25 n=75	0.5 n=73	1.0 n=70
at least 1 event	20 (24)	27 (36)	27 (37)	37 (53)
body as a whole	8 (10)	6 (8)	7 (10)	8 (11)
cardiovascular	5 (6)	14 (19)	12 (16)	14 (20)
digestive	10 (12)	10 (13)	6 (8)	14 (20)
heme and lymphatic	0	2 (3)	0	1 (1)
metabolic and nutritional	1 (1)	0	3 (4)	1 (1)
musculo-skeletal	0	1 (1)	0	0
nervous	5 (6)	4 (5)	2 (3)	4 (6)
respiratory	4 (5)	3 (4)	1 (1)	5 (7)
skin	5 (6)	1 (1)	2 (3)	2 (3)
special senses	0	0	1 (1)	1 (1)
urogenital	3 (4)	1 (1)	1 (1)	3 (4)

table P.4

More patients who received ibutilide reported an adverse event compared to patients who received placebo. The highest dose of ibutilide had the highest reporting rate and it was more than twice the reporting rate for placebo. The majority of reported events were in the body as a whole, cardiovascular, and digestive systems.

The adverse events that are shown below fulfill the following criteria: 1.) all events were reported by at least 2 ibutilide patients, and 2.) the percent of patients reporting the event was higher in at least 1 of the ibutilide dose groups compared to the placebo group.

Number and (percent) of patients

reported adverse event	placebo n=84	ibutilide			all ibutilide n=218
		0.25 n=75	0.5 n=73	1.0 n=70	
body as a whole					
chest pain	0	0	2 (3)	3 (4)	5 (2)
fever	1 (1)	2 (3)	1 (1)	2 (3)	5 (2)
headache	2 (2)	2 (3)	1 (1)	0	3 (1)
generalized edema	0	1 (1)	1 (1)	0	2 (1)
perioperative event	1 (1)	0	0	2 (3)	2(1)
cardiovascular					
ventricular extrasystoles	0	3 (4)	3 (4)	4 (6)	10 (5)
non sustained monomorphic VT (MMVT)	0	1 (1)	3 (4)	3 (4)	7 (3)
hypotension	1 (1)	3 (4)	1 (1)	2 (3)	6 (3)
heart arrest	0	3 (4)	0	1 (1)	4 (2)
non sustained polymorphic VT (PMVT)	1 (1)	0	0	3 (4)	3 (1)
a fibrillation	0	1 (1)	0	1 (1)	2 (1)
bradycardia	0	0	2 (3)	0	2 (1)
bundle branch block	0	0	2 (3)	0	2 (1)
phlebitis	0	1 (1)	1 (1)	0	2 (1)
sustained PMVT	0	0	0	2 (3)	2 (1)
digestive					
nausea	7 (8)	8 (11)	1 (1)	7 (10)	16 (7)
constipation	1 (1)	1 (1)	2 (3)	3 (4)	6 (3)
diarrhea	0	1 (1)	0	1 (1)	2 (1)
dyspepsia	0	0	1 (1)	1 (1)	2 (1)
heme and lymphatic					
anemia	0	2 (3)	0	0	2 (1)
respiratory					
wheezing	0	0	0	2 (3)	2 (1)

Table P.5

Ventricular extrasystoles, non sustained MMVT, non sustained PMVT, and sustained PMVT are events associated with ibutilide use.

Deaths

No deaths were reported.

Serious adverse events

A total of 8 serious events (in 6 patients) were reported and include:

atrial fibrillation: 1 (ibutilide 0.25 mg),
bradycardia: 1 (ibutilide 0.5 mg),
congestive heart failure: 1 (ibutilide 0.5 mg),
heart arrest: 2 (ibutilide 0.25 and 1 mg),
hypotension: 1 (ibutilide 0.5 mg),
sustained PMVT: 2 (ibutilide 1.0 mg).

Atrial fibrillation was reported in a 68 year old white male (#3147) with an ejection fraction of 45% and a history of myocardial infarction and angina. He converted to sinus rhythm after the 2nd dose of ibutilide 0.25 mg but relapsed into atrial fibrillation 2 days later.

Bradycardia, congestive heart failure, and hypotension were reported in a 48 year old white female (#3524) with a history of heart murmur, SOB, palpitations, and mitral valve commissurotomy. Ejection fraction was 55%. Her condition had been deteriorating prior to valve replacement. She converted to sinus rhythm after the 2nd dose of ibutilide 0.5 mg but relapsed into atrial fibrillation within 2 hours. She received a single dose of sotalol 80 mg and developed CHF, hypotension and bradycardia 2-3 hours later. The events resolved.

Heart arrest was reported in an 88 year old white male (#3140) who had a history of chest pain and dyspnea and had undergone CABG. Ejection fraction was 70%. He converted to sinus rhythm after the first 1 mg dose of ibutilide. About 1 day after the infusion, he experienced cardiac asystole and was resuscitated. Sick sinus syndrome was diagnosed and a pacemaker was implanted. Concomitant medication included lopressor and digoxin.

Heart arrest was reported in a 69 year old white male (#3027) who had a history of hypertension, SOB, palpitations, dyspnea on exertion, mitral regurgitation and coronary artery disease. He received a somewhat higher dose of study drug since there was no adjustment for his weight being under 60 kg (he received a total of 0.5 mg rather than 0.29 mg) and converted to sinus rhythm. He was treated with quinaglute about 8 hours after the ibutilide infusion and was found to be in ventricular fibrillation about 8 hours later. He was successfully defibrillated.

Sustained PMVT was reported in a 76 year old white female (#3362) with a history of myocardial infarction, angina and hypertension. She received a somewhat higher dose of study drug since there was no adjustment for her weight being under 60 kg (she received a total of 0.8 mg rather than 0.45 mg). During the end of the first infusion she developed sustained PMVT. The infusion was stopped and she was successfully treated with magnesium sulfate and pacing. QTc interval had increased 183 msec from

baseline to 583 msec at 30 minutes after start of infusion.

Sustained PMVT was reported in a 61 year old white female (#3751) who had a history of mitral stenosis, AV block, and frequent PACs. At the end of the 2 infusions of 1 mg ibutilide, she developed the arrhythmia and was given magnesium sulfate. She became hypotensive and was DC cardioverted. QTc interval was increased 197 msec from baseline to 634 msec at 30 minutes after start of infusion and 530 msec at hour 1.5.

A total of 7 patients, all of whom were randomized to ibutilide, discontinued study drug because of an adverse event. These events were

heart arrest: 1 (0.25 mg),
ventricular extrasystoles: 2 (0.5 and 1 mg),
non sustained MMVT: 3 (0.5 mg, 1 mg, 1 mg),
sustained PMVT: 1 (1.0 mg).

Heart arrest was reported in an 84 year old Hispanic female (#3239) who had a history of aortic stenosis. She received a higher dose of study drug than intended because there was no adjustment for her weight being under 60 kg (she received 0.25 mg rather than 0.14 mg). About 7 minutes into the first infusion, she had a 2-3 second sinus pause, the infusion was stopped, and she then converted to sinus rhythm. QTc interval was increased 9 msec from baseline to 408 msec.

Ventricular extrasystoles was reported in a 44 year old white male (#3363) who had a complicated history that included CAD, aortic stenosis/insufficiency, and alcohol abuse. About 5 minutes into his second infusion of 0.5 mg he developed frequent PVCs with couplets and triplets. The infusion was discontinued, the patient converted to sinus rhythm 14 minutes later, and then reverted to his index arrhythmia. QTc interval was increased 26 msec from baseline to 437 msec at 30 minutes after start of first infusion. The QTc interval at hour 1.5 was 423 msec.

Ventricular extrasystole was reported in a 66 year old white male (#3251) with a history of myocardial infarction and angina. Increased ventricular ectopy occurred during the first infusion of 1.0 mg so the second infusion was withheld. QTc interval was increased 119 msec from baseline to 507 msec at 30 minutes after start of drug infusion. The QTc interval at hour 1.5 was 457 msec.

Non sustained MMVT was reported in a 69 year old white female (#3032) who had a history of mitral stenosis. Prior to starting the second infusion of 1 mg, she developed episodic MMVT which continued for the next 8 hours despite drug discontinuation. She did not convert. QTc interval was increased 124 msec from baseline to 544 msec during the first episode of MMVT. The QTc interval at hour 1.5 was 425 msec.

Non sustained MMVT was reported in a 54 year old white male (#3085) with CAD 9 minutes into the second infusion of 0.5 mg. The infusion was stopped and the patient converted to sinus rhythm. QTc interval was increased 82 msec from baseline to 529 msec at study termination. The QTc interval at hour 1.5 was 577 msec.

Non sustained MMVT was reported in a 66 year old white male (#3528) with CAD half way through the second infusion of 0.5 mg. The infusion was stopped. The patient did not convert. QTc interval was

increased 20 msec from baseline to 437 msec at 30 minutes after the start of the first infusion. The QTc interval at hour 1.5 was 493 msec.

Sustained PMVT (#3362) was discussed in serious adverse event section.

Ventricular tachycardia

The following table shows all reported events.

	Number of events			
	placebo n=84	0.25 n=75	0.5 n=73	1.0 n=70
sustained PMVT	-	-	-	2
non sustained PMVT	1	-	-	3
non sustained MMVT	-	1	3	3

The following table discusses those patients with reported proarrhythmic events not leading to study drug discontinuation or classified as serious.

	study drug	age/race/sex	comment
non sustained PMVT			
3525	placebo	76/w/f	study drug failure, started procainamide, developed non sustained PMVT 27 hours after study drug infusion. QTc decreased from baseline
3536	ibutilide 1.0 mg	73/w/m	study drug failure, developed non sustained PMVT 5 minutes after study drug infusion. QTc increased from baseline by 104 msec to msec at minute 30
3691	ibutilide 1.0 mg	72/w/f	study drug success, developed non sustained PMVT 2 minutes after study drug infusion with repeated episodes the next day. QTc increased from baseline by 76 msec to 492 msec at termination. QTc at hour 1.5 was 506 msec
non sustained MMVT			
3093	ibutilide 1.0 mg	54/w/m	study drug failure, developed increased PVCs and then a 4 beat run of MMVT. QTc increased from baseline by 49 msec to 480 msec at termination. QTc at hour 1.5 was 435 msec
3148 -	ibutilide 0.25 mg	83/w/f	study drug success, developed short burst of MMVT 24 hours after infusion. QTc increased from baseline by 54 msec to 490 msec at termination.
3551	ibutilide 0.5 mg	67/w/m	study drug failure, developed episode of MMVT 2 days after infusion. QTc increased from baseline by 171 msec to 610 msec at minute 30. QTc at hour 1.5 was 473 msec
3741	ibutilide 0.5 mg	80/w/f	study drug failure, developed 6 beats of MMVT 5 hours after infusion. QTc increased from baseline by 102 msec to 490 msec at minute 30. QTc at hour 1.5 was 440 msec

QTc interval prolongation

The table below shows the mean QTc interval at baseline, at time of arrhythmia termination, and change from baseline at termination for the successes only.

Mean QTc (msec)

dose (n at baseline/n at termination)	baseline	termination n	change from baseline
placebo (13/13)	403	399	-3
ibutilide 0.25 mg (29/30)	413	438	26
ibutilide 0.5 mg (34/30)	404	452	47
ibutilide 1.0 mg (40/39)	414	474	60

Table K.29

Increasing doses of ibutilide resulted in increased QTc prolongation.

The table below shows the mean QTc intervals measured at baseline, at 30 minutes after the start of study drug infusion, and change from baseline at minute 30 for failures only.

QTc interval (msec)

dose (n at baseline/n at termination)	baseline	minute 30	change from baseline
placebo (71/71)	414	424	10
ibutilide 0.25 mg (45/44)	416	454	38
ibutilide 0.5 mg (38/38)	411	458	50
ibutilide 1.0 mg (28/30)	415	486	67

table K.33

Ibutilide prolonged the QTc interval for the failures as well, and there was a dose response.

Ibutilide had no effect on other ECG intervals.

DC cardioversion

The mean number of attempts at DC cardioversion was similar for all treatment groups and ranged from 1.0 to 1.5 (table L.13). The mean number of joules used was also similar for the treatment groups (table L.16). Although the number of patients who underwent attempts at DC cardioversion was small (n=23), there is no indication that use of ibutilide requires modification of DC cardioversion.

Vital signs

There is no indication that the use of ibutilide adversely affects blood pressure. There were statistically significant decreases in heart rate in all treatment groups including placebo (table M.3.3), probably reflecting the effect of conversion on slowing heart rate. While the overall changes were small, study patients with heart rates less than 60 bpm were generally not included in the trial.

Laboratory

Blood samples for hematology and chemistry as well as urine samples were obtained for analysis pretreatment and at hour 24. The patients had all undergone recent cardiac surgery so the value of the results in regards to use of ibutilide is questionable. However, there is no indication that ibutilide affects any laboratory value adversely. This is consistent with the findings in the NDA and safety update.

Summary

Infusions of ibutilide 0.5 and 1.0 mg were highly effective, compared to placebo, in terminating atrial flutter (afl), especially, and atrial fibrillation (afib) in patients who developed their arrhythmia shortly after cardiac surgery. Although ibutilide 0.25 mg was not significantly different from placebo in terminating afib, this dose was highly effective in terminating afl. The majority of successes converted to normal sinus rhythm and the majority remained converted at least through hour 24. This study found that the higher the dose of ibutilide used, the less likely patients needed more than 1 infusion in order to convert.

More patients who received ibutilide reported an adverse event compared to patients who received placebo. The highest dose of ibutilide had the highest reporting rate and it was more than twice the reporting rate for placebo. The majority of reported events were in the body as a whole, cardiovascular, and digestive systems. There is a strong association between ibutilide use and the occurrence of ventricular extrasystoles, non sustained monomorphic ventricular tachycardia, non sustained polymorphic ventricular tachycardia, and sustained polymorphic ventricular tachycardia. Increasing doses of ibutilide resulted in increased QTc prolongation.

No deaths were reported in this study. Serious adverse events, all reported by patients on ibutilide, included atrial fibrillation, bradycardia, congestive heart failure, heart arrest, hypotension, and sustained polymorphic ventricular tachycardia. Of the patients who discontinued study drug because of an adverse event, all were on ibutilide. These events were heart arrest, ventricular extrasystoles, non sustained monomorphic ventricular tachycardia, and sustained polymorphic ventricular tachycardia.

This study showed that ibutilide infusions were effective in converting patients who developed afl or afib after recent cardiac surgery. The adverse events in this study included QTc prolongation and ventricular arrhythmias, well known to be associated with ibutilide use.