

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20491/S001

CHEMISTRY REVIEW(S)

JAN 7 1998

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 20-491
3. Name and Address of Applicant (City & State) The Upjohn Company 7000 Portage Road Kalamazoo, MI 49001		4. Supplement(s) Number(s) Date(s) S-001 2/13/96 (LR)	
5. Drug Name CORVERT Injection	6. Nonproprietary Name Ibutilide fumarate		8. Amendments & Other (reports, etc) - Dates LR - 12/19/97
7. Supplement Provides For: Revised package insert.			
9. Pharmacological Category Treatment of atrial fibrillation and flutter	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 0.1 mg/mL		
14. Chemical Name and Structure		15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No	
16. Comments: The revision affects the Clinical Studies, Adverse Reactions and Dosage and Administration sections and consists of additional information on post-cardiac surgery patients treated with CORVERT. Supporting data is included. Satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
17. Conclusions and Recommendations: Satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
18. REVIEWER			
Name Danute G. Cunningham		Date Completed January 6, 1998	
Distribution: <input checked="" type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO <input type="checkbox"/> District			

20491S01.AM1

[Handwritten signature] 1/7/98

NOV 25 1998

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 20-491
3. Name and Address of Applicant (City & State) Pharmacia & Upjohn Company 7000 Portage Road Kalamazoo, MI 49001		4. Supplement(s) Number(s) Date(s) SE8-001 11/3/98 (BL) AL	
5. Drug Name CORVERT Injection	6. Nonproprietary Name Ibutilide fumarate		8. Amendments & Other (reports, etc) - Dates 12/19/97; 2/13/98
7. Supplement Provides For: Revised package insert.			
9. Pharmacological Category Treatment of atrial fibrillation and flutter	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/NDA(s)/DMF(s)
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 0.1 mg/mL		
14. Chemical Name and Structure Methanesulfonamide, N-(4-(4-(ethylheptylamino)-1-hydroxybutyl)phenyl), (+) (-), (E)-2-butenedioate (1:0.5) (hemifumarate salt)			15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No
16. Comments: The revision affects the Clinical Studies, Adverse Reactions and Dosage and Administration sections. No changes in DESCRIPTION and HOW SUPPLIED sections.			
17. Conclusions and Recommendations: Satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
18. REVIEWER			
Name Danute G. Cunningham		Date Completed November 23, 1998	
Distribution: <input checked="" type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO			

20491S01.AM2

11-23-98

201

APR 5 1999

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 20-491
3. Name and Address of Applicant (City & State) Pharmacia & Upjohn Company 7000 Portage Road Kalamazoo, MI 49001		4. Supplement(s) Number(s) Date(s) SE8-001 2/25/99 (AF)	
5. Drug Name CORVERT Injection	6. Nonproprietary Name Ibutilide fumarate		8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Final printed labeling.			
9. Pharmacological Category Treatment of atrial fibrillation and flutter	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/NDA(s)/DMF(s)
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 0.1 mg/mL		
14. Chemical Name and Structure Methanesulfonamide, N-(4-(4-(ethylheptylamino)-1-hydroxybutyl)phenyl), (+) (-), (E)-2-butenedioate (1:0.5) (hemifumarate salt)		15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No	
16. Comments: Insert - 816 418 003B 691659 Revised December 1998 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
17. Conclusions and Recommendations: Satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
18. REVIEWER			
Name Danute G. Cunningham			Date Completed March 16, 1999
Distribution: <input checked="" type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO			

20491S01.AM3

4-2-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20491/S001

ADMINISTRATIVE DOCUMENTS

MEMO TO THE FILE

JAN 21 1998

Application: NDA 20-491
Sponsor: The Upjohn Company
Product: Corvert (ibutilide fumarate) Injection
Regarding: S-001

JAN 21 1998

Supplement 001 was received on December 22, 1997 without a User Fee Cover Sheet (Form FDA 3397). Ms. Zelda McDonald completed the internal user fee cover form and specified that the supplement contains clinical data. An attempt by Ms. McDonald to contact Mr. James Chambers at Pharmacia and Upjohn (P & U) regarding the submission of a User Fee Cover Sheet for this supplement was unsuccessful because the firm was closed for the holiday season.

On January 5, 1997, Ms. Diana Willard contacted Mr. Chambers and stated that she believed this supplement was subject to User Fees because it contained "Clinical data that do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling)." It was further noted that P & U's cover letter for this supplement states that "Data in support of this revision are contained in Pharmacia & Upjohn study report (TR) 1016-97-001, ..." Ms. Willard requested that a User Fee Cover Sheet be submitted. Mr. Chambers stated that he would talk with Mr. Robert Paarlberg of P & U regarding the assessment of an User Fee for this supplement. He further stated that a User Fee Cover Sheet would be submitted.

Ms. Willard contacted Mr. Chambers again on January 7, 1997 regarding P & U's decision on the assessment of User Fees for NDA 20-491/S-001. Mr. Chambers stated that P & U does not believe this supplement is subject to User Fees. A letter submitted January 9, 1997 states that "the proposed revisions to the labeling provide information on the use of a lower dose of ibutilide fumarate in post-cardiac surgery patients. This group of patients represents a cohort of the approved population of patients with atrial fibrillation and atrial flutter. As such, these changes modify the labeling to improve the safe use of CORVERT Injection."

Ms. Willard then spoke with Ms. Morgenstern regarding this supplement. It was agreed that Mr. Tom Hassall, Senior Program Manager, be consulted. Mr. Hassall concurred with Ms. Willard that a User Fee should be paid for this supplement.

Ms. Willard spoke with Mr. Chambers of Pharmacia and Upjohn on January 15, 1998 and relayed the Agency's decision that a User Fee should be paid for this supplement. Mr. Chambers stated that P & U will pay the appropriate User Fee. In view of this agreement and the elapsed time from the receipt of the submission, it was decided that an "UN" letter will not be issued.

Diana Willard
Regulatory Health Project Manager

**RHPM Review of Final Printed Labeling
NDA 20-491/S-001**

Sponsor: The Upjohn Company
Product: Corvert (ibutilide fumarate) Injection
Submission Date: December 19, 1997
Receipt Date: December 22, 1997
Type of Submission: Draft Labeling

Background: Supplement 001 provides for revisions to the **CLINICAL PHARMACOLOGY/Clinical Studies, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections of the labeling to add information regarding use of Corvert in post-cardiac surgery patients.

Evaluation: When compared with the most recently approved package insert dated August 1997, the following changes were noted:

1) Under **CLINICAL PHARMACOLOGY/Clinical Studies**, the following changes were made:

a) The first sentence of the second paragraph was changed from:

Patients in clinical trials were hemodynamically stable.

to:

Patients in registration trials were hemodynamically stable.

b) The following paragraph was added at the end of this subsection:

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%.

2) The following paragraph was added at the end of the **ADVERSE REACTIONS** section:

In the post-cardiac surgery study (see CLINICAL STUDIES), similar types of medical

events were reported. In the 1 mg ibutilide fumarate treatment group (N=70), 2 patients (2.9%) developed sustained polymorphic ventricular tachycardia and 2 other patients (2.9%) developed nonsustained polymorphic ventricular tachycardia. Polymorphic ventricular tachycardia was not reported in the 73 patients in the 0.5 mg dose group or in the 75 patients in the 0.25 mg dose group.

- 3) Under **OVERDOSAGE/Human Experience**, the first sentence was changed from:

In the clinical trials with CORVERT Injection, four patients were unintentionally overdosed.

to:

In the registration trials with CORVERT Injection, four patients were unintentionally overdosed.

- 4) Under **DOSAGE AND ADMINISTRATION**, the following paragraph was added following the second paragraph in the section:

In the post-cardiac surgery study (see CLINICAL STUDIES), one or two intravenous infusions of 0.5 mg (0.005 mg/kg per dose for patients weighing less than 60 kg) was effective in terminating atrial fibrillation or atrial flutter.

- 5) Under **HOW SUPPLIED**, "The Upjohn Company" was changed to "Pharmacia & Upjohn Company."

Comments/Recommendations: In her January 7, 1998 review, the chemist states that the labeling is satisfactory for the **DESCRIPTION** and **HOW SUPPLIED** sections.

Dr. Lipicky wrote (see attached) that a sentence stating "The majority (53% to 72%) of patients converted to sinus rhythm remained in sinus rhythm for 24 hours" should be added to the end of the paragraph under 1b above.

An approvable letter that incorporates Dr. Lipicky's requested change to the sponsor's proposed labeling should issue.

Diana M. Willard
Regulatory Health Project Manager

cc: original file
HFD-110
HFD-110/DWillard
HFD-110/SBenton
HFD-2/MedWatch

NOV 19 1998

**RHPM Review of Draft Labeling
NDA 20-491/S-001**

Sponsor: Pharmacia & Upjohn Company
Product: Corvert (ibutilide fumarate) Injection
Submission Date: November 3, 1998
Receipt Date: November 4, 1998
Type of Submission: Draft Labeling

Background: Supplement 001, submitted on December 19, 1997, provides for revisions to the **CLINICAL PHARMACOLOGY/Clinical Studies**, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the labeling to add information regarding use of Corvert in post-cardiac surgery patients. An approvable letter issued July 2, 1998. This letter requested that the sponsor add the statement "The majority (53% to 72%) of patients converted to sinus rhythm remained in sinus rhythm for 24 hours" at the end of the **CLINICAL PHARMACOLOGY/Clinical Studies** subsection. A September 1, 1998, facsimile transmission (FAX) from Pharmacia & Upjohn proposed to change this sentence to "The majority (63%) of patients converted with ibutilide fumarate remained in sinus rhythm for 24 hours." The Division disagreed and a teleconference was held on October 19, 1998 to discuss wording a statement that both Pharmacia & Upjohn and the Division could agree upon. Following this teleconference, Pharmacia & Upjohn sent an October 20, 1998 FAX proposing that the statement "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" be used. The Division stated that this statement was acceptable with one minor change. The first time the word "to" appears, it should be changed to "and." Ms. Kreiger from Pharmacia & Upjohn agreed to this change during an October 28, 1998 telephone conversation with Ms. Willard of the Division.

Evaluation: When compared with the draft labeling that issued with the July 2, 1998 approvable letter for this supplement, the following change was noted:

- 1) Under **CLINICAL PHARMACOLOGY/Clinical Studies**, the last sentence of this subsection has been changed from:

The majority (53% to 72%) of patients converted to sinus rhythm remained in sinus rhythm for 24 hours.

to:

The majority of patients (53% to 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.

Comments/Recommendations: An approvable letter should issue.

Diana M. Willard
Regulatory Health Project Manager

cc: original
HFD-110
HFD-110/Dwillard
HFD-110/SBenton

MAY 13 1999

RHPM Review of Final Printed Labeling
NDA 20-491/S-001

Sponsor: Pharmacia & Upjohn Company
Product: Corvert (ibutilide fumarate) Injection, 0.1 mg/ml
Date of Submission: February 25, 1999
Date of Receipt: March 1, 1999
Type of Submission: Final Printed Labeling

Background: Supplement 001, submitted on December 19, 1997, provides for revisions to the **CLINICAL PHARMACOLOGY/Clinical Studies**, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the labeling to add information regarding use of Corvert in post-cardiac surgery patients. An approvable letter issued July 2, 1998. This letter requested that the sponsor add the statement "The majority (53% to 72%) of patients converted to sinus rhythm remained in sinus rhythm for 24 hours" at the end of the **CLINICAL PHARMACOLOGY/Clinical Studies** subsection. A September 1, 1998, facsimile transmission (FAX) from Pharmacia & Upjohn proposed to change this sentence to "The majority (63%) of patients converted with ibutilide fumarate remained in sinus rhythm for 24 hours." The Division disagreed and a teleconference was held on October 19, 1998 to discuss wording a statement that both Pharmacia & Upjohn and the Division could agree upon. Following this teleconference, Pharmacia & Upjohn sent an October 20, 1998 FAX proposing that the statement "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" be used. The Division stated that this statement was acceptable with one minor change. The first time the word "to" appears, it should be changed to "and." Ms. Kreiger from Pharmacia & Upjohn agreed to this change during an October 28, 1998 telephone conversation with Ms. Willard of the Division.

On November 3, 1998, Pharmacia & Upjohn submitted draft labeling revised to reflect the wording agreed upon during the October 28, 1998 telephone conversation. An approvable letter issued for this draft labeling on November 19, 1998.

Evaluation: When compared with the draft labeling submitted on November 3, 1998, the following changes were noted:

- 1) Throughout the labeling, the term "clinical studies" has been changed to "registration studies."
- 2) The "**Caution:** Federal Law prohibits dispensing without prescription" statement under **HOW SUPPLIED** has been replaced with "Rx only."

Comments/Recommendations: The change under 1 above is acceptable to the medical officer. The change under 2 above is provided for under the FDA Modernization Act of 1997.

An approval letter should issue for this supplement.

Diana M. Willard
Regulatory Health Project Manager

cc: originals
HFD-110
HFD-110/SBenton
HFD-110/DWillard
HF-2/MedWatch

OCT 19 1998

**Minutes of a Teleconference
October 19, 1998**

Application: NDA 20-491
Corvert (ibutilide fumarate) Injection

Sponsor: Pharmacia & Upjohn

Attending:

Pharmacia & Upjohn:

James VanderLugt, M.D.	Clinical Research Manager
Kimberly T. Perry, Ph.D.	Biostatistician, Clinical Biostatistics I
Roberta Kreiger	Senior Regulatory Manager
Rebecca Tong	Regulatory Affairs

FDA:

Shaw Chen, M.D., Ph.D.	Team Leader/Medical, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Diana Willard	Regulatory Health Project Manager, HFD-110

Background: SE8-001, submitted on December 19, 1997, provided 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. An approvable letter issued July 2, 1998 requesting final printed labeling "identical in content to the enclosed marked-up draft." In a September 1, 1998 facsimile transmission (FAX), Pharmacia & Upjohn (P & U) proposed to change the statement "The majority (53% to 72%) of patients converted to sinus rhythm remained in sinus rhythm for 24 hours" under **CLINICAL PHARMACOLOGY/Clinical Studies** to "The majority (63%) of patients converted with ibutilide fumarate remained in sinus rhythm for 24 hours." On September 3, 1998, Ms. Willard spoke with Ms. Kreiger and conveyed the message that Drs. Chen and Gordon preferred that the wording of this sentence not be changed. Ms. Kreiger stated that P & U would send a FAX further outlining their position. A FAX was not sent. On October 16, 1998, Ms. Kreiger called and requested a teleconference to discuss the wording for this sentence.

Teleconference: Dr. Vanderlugt began by stating that the majority (63%) of patients converted with ibutilide fumarate remained in sinus rhythm for 24 hours. Dr. Gordon replied that her original review of the supplement indicated that 53% of patients receiving 0.5 mg and 72% of patients receiving 1.0 mg remained in the converted rhythm through hour 24. Dr. Vanderlugt stated the P & U would like to clarify in the labeling that the

53% is associated with the 0.5 mg dose and the 72% is associated with the 1.0 mg dose. It is acceptable to the Division to qualify or describe the dosed population in more detail.

P & U will send by facsimile transmission a proposed new statement that details the percentage of patients at the 0.5 and 1.0 mg doses that converted to and remained in sinus rhythm for 24 hours. A statement will also be added to indicate that the patients in this study did not receive additional maintenance therapy.

Addendum: A FAX (attached) was received from P & U on October 21, 1998. Dr. Gordon stated that the wording proposed in the FAX was acceptable with one minor change. In the first sentence, the first time the word "to" appears, it should be changed to "and." Ms. Willard conveyed this message to Ms. Kreiger during an October 28, 1998 telephone conversation. Ms. Kreiger stated that this would be an acceptable change.

Signature, Minutes Preparer _____ Diana Willard

Concurrence, Meeting Chair _____ Shaw Chen, M.D.

cc: original
HFD-110
HFD-110/DWillard
HFD-110/SBenton

Drafted: 10/22/98
RD: Chen 10/23/98
Gordon 10/23/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20491/S001

CORRESPONDENCE

ORIGINAL



Pharmacia & Upjohn

Office of:
James H. Chambers
Regulatory Manager
U.S. Regulatory Affairs

Telephone No. (616) 833-1397
Facsimile No. (616) 833-8237

December 19, 1997

Division of Cardio-Renal Drug Products HFD-110
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA NO. 20-491 REF. NO. 001
NDA SUPPL FOR. SLR SE8 - 001

Re: NDA 20-491
CORVERT® Injection
(ibutilide fumarate injection)



Labeling Supplement

Dear Sir/Madam:

We are supplementing the above cited NDA under the provisions of §314.70(b)(3) to provide for a revised package insert (Attachment 1).

The revision affects the Clinical Studies, Adverse Reactions, and Dosage and Administration sections and consists of additional information on post-cardiac surgery patients treated with CORVERT. Data in support of this revision are contained in Pharmacia & Upjohn study report (TR) 1016-97-001, "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 (Protocol M/7550/0017)." A copy of the complete study report, including appendices was submitted to _____ April 9, 1997.

A minor change, consisting of replacing the description "clinical studies" with "registration studies", has been made in several other sections of the insert to clarify the study source of the information described.

If you have any questions regarding the contents of this submission, please contact James H. Chambers at (616) 833-1397. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

James H. Chambers, Regulatory Manager

JHC:crdt/Attachments
Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

ORIGINAL

I would add one sentence (page 2 of P 2). Check it out with Mary Ann. otherwise O.K. get letter ready.

rec'd from Dr. H. P. Kelly 6/24/98



ORIGINAL

Pharmacia & Upjohn

Office of:
James H. Chambers
Regulatory Manager
U.S. Regulatory Affairs

Telephone No. (616) 833-1397
Facsimile No. (616) 833-8237

December 19, 1997

Division of Cardio-Renal Drug Products HFD-110
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA NO. 20-491 REF. NO. 001
NDA SUPPL FOR. SLR

Re: NDA 20-491
CORVERT® Injection
(ibutilide fumarate injection)



Labeling Supplement

Dear Sir/Madam:

We are supplementing the above cited NDA under the provisions of §314.70(b)(3) to provide for a revised package insert (Attachment 1).

The revision affects the Clinical Studies, Adverse Reactions, and Dosage and Administration sections and consists of additional information on post-cardiac surgery patients treated with CORVERT. Data in support of this revision are contained in Pharmacia & Upjohn study report (TR) 1016-97-001, "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 (Protocol M/7550/0017)." A copy of the complete study report, including appendices was submitted to _____ April 9, 1997.

A minor change, consisting of replacing the description "clinical studies" with "registration studies", has been made in several other sections of the insert to clarify the study source of the information described.

If you have any questions regarding the contents of this submission, please contact James H. Chambers at (616) 833-1397. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

James H. Chambers, Regulatory Manager

JHC:crdt/Attachments
Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

ORIGINAL



Pharmacia & Upjohn

Office of:
James H. Chambers
Regulatory Manager
U.S. Regulatory Affairs

Telephone No. (616) 833-1397
Facsimile No. (616) 833-8237

January 8, 1998

Division of Cardio-Renal Drug Products HFD-110
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

~~SUPPL. LABELING~~
SNC to
S-001



Re: NDA 20-491
CORVERT® Injection
(ibutilide fumarate injection)

Dear Sir/Madam:

In response to a request from Dianna Willard, Regulatory Health Project Manager, on January 5, 1998, Pharmacia & Upjohn is enclosing a User Fee Cover Sheet for the NDA 20-491, CORVERT Injection, Labeling Supplement which was inadvertently omitted in the original submission on December 19, 1997.

It is the position of Pharmacia & Upjohn that this labeling supplement does not contain clinical data as it applies to the assessment of User Fees. The proposed revisions to the labeling provide information on the use of a lower dose of ibutilide fumarate in post-cardiac surgery patients. This group of patients represents a cohort of the approved population of patients with atrial fibrillation and atrial flutter. As such, these changes modify the labeling to improve the safe use of CORVERT Injection.

If you have any questions regarding the contents of this submission, please contact James H. Chambers at (616) 833-1397. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in cursive script, appearing to read "Jim Chambers".

James H. Chambers
Regulatory Manager

JHC:SEH
Attachments



ORIGINAL
Pharmacia & Upjohn

Office of:
Roberta A. Krieger
Senior Regulatory Manager
Regulatory Affairs

Telephone No. (616) 833-8162
Facsimile No. (616) 833-8237

February 2, 1998

Division of Cardio-Renal Drug Products HFD-110
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

GENERAL CORRESP
SNC to S001

Re: NDA 20-491
CORVERT® Injection
(ibutilide fumarate injection)

General Correspondence
Revised User Fee Cover Sheet



Dear Sir/Madam:

In response to our General Correspondence dated January 8, 1998, Pharmacia & Upjohn has been notified by Dianna Willard, Regulatory Health Project Manager, that the Labeling Supplement dated December 19, 1997, does contain clinical data as it applies to the assessment of User Fees. A revised User Fee Cover Sheet is enclosed. A check in the amount of _____ has been mailed to Mellon Bank.

If you have any questions regarding the contents of this submission, please contact Roberta A. Krieger at (616) 833-8162. Please send correspondence addressed to Unit 7025-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Roberta A. Krieger, Senior Regulatory Manager
Regulatory Affairs

RAK:SEH
Attachments

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

ORIGINAL

ORIGINAL



Pharmacia & Upjohn

Office of:
Roberta A. Krieger
Senior Regulatory Manager
Regulatory Affairs

Telephone No. (616) 833-8162
Facsimile No. (616) 833-8237

July 10, 1998

Division of Cardio-Renal Drug Products HFD-110
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building 5th Floor
Rockville, Maryland 20852



PL NEW CORRE

(L)

SE8-001

RE: NDA 20-491/S-001
CORVERT® Injection
(Ibutilide fumarate injection)

General Correspondence

Sir/Madam:

Please refer to your letter dated July 2 1998, (received July 10, 1998), in which you informed us that our labeling supplement NDA 20-491/S-001 is approvable. We note that before this application will be approved it will be necessary for us to submit final printed labeling for the drug. Please be advised it is our intention to amend the supplemental application as soon as possible to provide the final labeling identical in content to the marked up draft enclosed in your letter of July 2, 1998.

If you have any questions regarding this information please contact me at (616) 833-8162.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Roberta A. Krieger
Regulatory Affairs

RAK:kmv
Enclosures

NDA 20-491



Pharmacia & Upjohn

SEP - 1 1998

To: Diana Willard, Cardio-Renal	
Fax No: 301-594-5494	
From: Roberta Krieger	
Tel No: 616-833-8162	Fax No: 616-833-0409
Date: September 1, 1998	Pages (including this one): 2

NDA 20-491/S-001 CORVERT Injection

Dear Diana,

July 10, 1998 we received the approvable letter for our labeling supplement NDA 20-491/S-001 (dated July 2, 1998). When we first received the letter it was our intention to implement the exact wording specified in the letter and simply provide the final printed labeling. We confirmed this to you in our letter of July 10, 1998. However, when our statistician reviewed the revised text she suggested a slight rewording of the one sentence added by the division.

A single percentage is proposed (rather than a range) to avoid implying that the range is directly correlated with the different dose groups. We also prefer to add "with ibutilide" because the percentage applies to active treatment groups, not placebo.

Our proposal is to change the text **From:**

"The majority (53% to 72%) of patients converted to sinus rhythm remained in sinus rhythm for 24 hours".

depending upon study

PHARMACIA & UPJOHN, 7000 Portage Road, Kalamazoo, MI 49001

Confidentiality Note: The documents accompanying this telecopy transmission contain information belonging to Pharmacia & Upjohn, which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us. Thank you.

To:

"The majority (63%) of patients converted with ibutilide fumarate remained in sinus rhythm for 24 hours."

May I ask you to check the acceptability of this suggestion with Dr. Gordon? If she has no objections we will submit the proposed revision formally.

Thank you for your assistance.

Sincerely,

Roberta

9/3/98 I spoke with Roberta Kreiger today and relayed the message that Drs Gordon and Chen prefer that the wording not be changed. Ms. Kreiger stated that P & U will send a FAX further outlining their position.

PHARMACIA & UPJOHN, 7000 Portage Road, Kalamazoo, MI 49001

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NDA 20-491

OCT 20 1998



Pharmacia & Upjohn

To: Diana Willard, Cardio-Renal	
Fax No: 301-594-5494	
From: Roberta Krieger	
Tel No: 616-833-8162	Fax No: 616-833-0409
Date: October 20, 1998	Pages (including this one): 2

NDA 20-491/S-001 CORVERT Injection

Dear Diana,

This is to confirm our telephone discussion Monday, October 20, regarding revised labeling for CORVERT. The discussion referred to text in the approvable letter for our labeling supplement NDA 20-491/S-001 (dated July 2, 1998).

Based on the comments of Dr. Gordan and Dr. Shaw we have drafted the following:

Our proposal is to change the text **From:**

"The majority (53% to 72%) of patients converted to sinus rhythm remained in sinus rhythm for 24 hours".

To:

"The majority of patients (53% to 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."

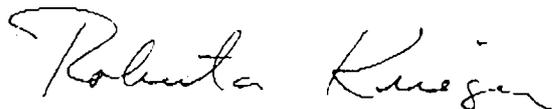
PHARMACIA & UPJOHN, 7000 Portage Road, Kalamazoo, MI 49001

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May I ask you to check the acceptability of this suggestion with Dr. Gordon and Dr. Shaw?
If there no objections we will submit the proposed revision formally.

Thank you for your assistance.

Sincerely,



PHARMACIA & UPJOHN, 7000 Portage Road, Kalamazoo, MI 49001

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ORIGINAL

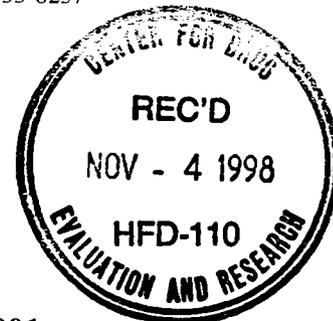
Pharmacia & Upjohn

Office of:
Roberta A. Krieger
Acting Director
Regulatory Affairs

Telephone No. (616) 833-8162
Facsimile No. (616) 833-8237

November 3, 1998

Division of Cardio-Renal Drug Products HFD-110
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building 5th Floor
Rockville, Maryland 20852



~~NOT REPLY AMEND~~

SE8-001
(BL)AL (par 50)

RE: NDA 20-491/S-001
CORVERT®
(Ibutilide Fumarate Injection)

Amendment to Supplement /S-001

Sir/Madam:

We are amending the above cited supplement to provide a proposed revised package insert. This supplement, submitted on December 19, 1997, requested the addition of information in the insert on the use of ibutilide fumarate in post-cardiac surgery patients. This supplement was found approvable, with modification of the new paragraph in the Clinical Pharmacology section, on July 2, 1998.

The FDA requested modification consisted of the addition of the following sentence at the end of the new paragraph: "The majority (53% to 72%) of patients converted to sinus rhythm remained in sinus rhythm for 24 hours." Because we felt this message could be made clearer, we provided an alternative sentence by fax on October 20, 1998. That statement, with one modification requested by FDA in a conversation between Diana Willard and Roberta Krieger on October 28, 1998, is as follows: 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."

We plan to proceed to prepare final printed inserts reflecting the attached text and will submit the final printed labeling (FPL) to complete the approval process as requested in the FDA approvable letter of July 2, 1998.

If you have any questions regarding the contents of this submission, please contact Roberta A. Krieger at (616) 833-8162. Please send correspondence addressed to Unit 7025-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in cursive script that reads "Roberta Krieger".

Roberta A. Krieger, Acting Director
Regulatory Affairs

RAK:SEH
Enclosures



Pharmacia & Upjohn

ORIGINAL

Office of:
Rebecca K. Tong, M.S. **SUPPL. NEW CORRESP**
Regulatory Manager
Regulatory Affairs **(SNC)**

Telephone No. (616) 833-0286
Facsimile No. (616) 833-8237

December 2, 1998

Division of Cardio-Renal Drug Products HFD-110
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building 5th Floor
Rockville, Maryland 20852



RE: NDA 20-491/S-001
CORVERT®
(Ibutilide Fumarate Injection)

General Correspondence

Dear Dr. Lipicky:

Please refer to your approvable letter dated November 19, 1998 (received on December 1, 1998) regarding the above referenced Supplemental NDA.

The purpose of this letter is to notify the Agency that we intend to file an amendment to the sNDA when the final printed labeling is available.

If you have any questions regarding the contents of this submission, please contact Rebecca K. Tong at (616) 833-0286. Please send correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Rebecca K. Tong, M.S.
Regulatory Manager
Regulatory Affairs

RKT/crdt

Enclosure

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000



Pharmacia & Upjohn

ORIGINAL

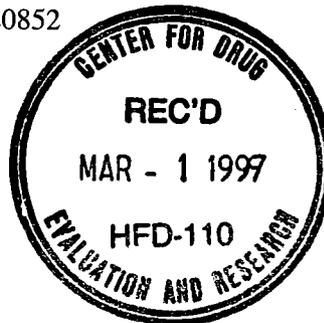
Office of:
Rebecca K. Tong, MS
Regulatory Manager
Regulatory Affairs

Telephone No. (616) 833-0286
Facsimile No. (616) 833-8237

February 25, 1999

Division of Cardio-Renal Drug Products HFD-110
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building 5th Floor
Rockville, Maryland 20852

NDA SUPPL AMEND
SEB-001
(AF)



RE: NDA 20-491/S-001
CORVERT®
(Ibutilide fumarate injection)

FINAL PRINTED LABELING

Dear Sir/Madam:

We are providing 20 copies of the final printed insert in response to the approvable letter for the above cited supplement dated November 19, 1998 (Attachment 1). The insert is identified as code 816 418 003. As requested, we are also providing a marked up copy of the insert currently in use (left column) with the changes shown on the right (Attachment 2).

As you will note, the attached final printed insert correctly contains the statement "For intravenous infusion only" under the product titles consistent with the initially approved labeling for this product. In preparing the attached final printed insert we became aware that it had been inadvertently deleted from the version currently in use.

We look forward to your approval of this NDA supplement.

If you have any questions, please contact Rebecca K. Tong at (616) 833-0286. Please send correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY


Rebecca K. Tong, MS
Regulatory Affairs

RKT:lmf

Enclosures

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

MAY 20 1998



Facsimile Transmittal

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

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Transmitted to FAX number: 616-833-8237

Attention: James H. Chambers

Company name: Pharmacia & Upjohn

Phone:

Subject: Antibiotic

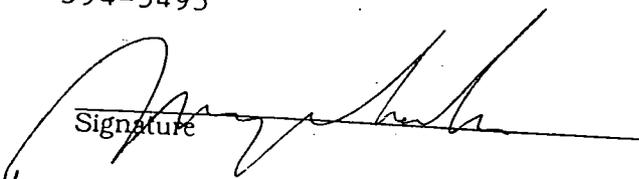
Date: 3-5-98

Pages including this sheet: 2

From: M Gardner

Phone: (301) 594-5321

FAX: (301) 594-5494 or
594-5495


Signature

See attached

cc: IND/NDA 20-491
HFD-110
HFD-111/CSO

Study report 1016-97-001

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

Please explain if the patients who did not remain in converted rhythm at 24 hours were those with a history of afib/aflutter (i.e., prior to cardiac surgery). How many patients did you enroll with this history?

Thanks