Pfizer Inc.
235 East 42nd St.
New York, NY 10017

May 2016

Dosing Error in Published ASHP Book Involving Corvert® (ibutilide fumarate injection)

Dear Healthcare Provider,

The purpose of this letter is to inform you of an important dosing error in a published book involving Corvert® (ibutilide fumarate injection), an antiarrhythmic drug approved for the rapid conversion of atrial fibrillation or atrial flutter of recent onset to sinus rhythm.

In April 2016, The Division of Cardiovascular and Renal Products of the Food and Drug Administration (FDA) was made aware of a dosing error in an American Society of Health-System Pharmacists (ASHP) book entitled *Demystifying Drug Dosing in Obese Patients* and published in February 2016 in paper and digital copy. The error involves the drug ibutilide fumarate injection, and is a ten-fold dosing error. ASHP is taking steps to inform their members and others who have purchased the book.

In immediate correspondence with the FDA, Pfizer has conducted a Global Safety Database search to identify any potential or confirmed cases of overdose that could be related to this error. The search included all ibutilide cases received since IBD (28-Dec-1995) through 29-Apr-2016 and confirmed that there were no overdose cases up to this date with referral to an obese patient who received a 10-fold overdose.

Pfizer will continue to work with the FDA to monitor any reported cases of overdose and will communicate any new information to healthcare providers.

Details of the corrected section in the published ASHP book entitled *Demystifying Drug Dosing in Obese Patients* by Brandon R. Shank and David E. Zimmerman was on page 84, Chapter 4 – Critical Care, *under the heading "Ibutilide" where dosing appeared inaccurately as "10 mg (one vial)."*

The corrected version of the paragraph is as follows:

> Ibutilide is a Vaughan-Williams Class III antiarrhythmic indicated for the rapid conversion of atrial fibrillation or atrial flutter.[35] The dosing for ibutilide recommends **1 mg** IV infusion over 10 minutes for patients who weigh 60 kg or more.[35] A second infusion of **1 mg** can be given 10 minutes later if the arrhythmias did not terminate. No other data are available for dosing in obese patients, and the above dosing of **1 mg** should be used.

Dosage and Administration for Corvert® in approved Full Prescribing Information is as follows:

The recommended dose based on controlled trials is outlined in the Table below. Ibutilide infusion should be stopped as soon as the presenting arrhythmia is terminated or in the event of sustained or nonsustained ventricular tachycardia, or marked prolongation of QT or QTc.

Recommended Dose of CORVERT Injection

Patient Weight	*Initial Infusion (over 10 minutes)*	*Second Infusion*
60 kg (132 lb) or more	*One vial (1 mg ibutilide fumarate)*	*If the arrhythmia does not terminate within 10 minutes after the end of the initial infusion, a second 10-minute infusion of equal strength may be administered 10 minutes after completion of the first infusion.*
Less than 60 kg (132 lb)	*0.1 mL/kg (0.01 mg/kg ibutilide fumarate)*	

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. Skilled personnel and proper equipment, such as a cardioverter/defibrillator, and medication for treatment of sustained ventricular tachycardia, including polymorphic ventricular tachycardia, must be available during administration of CORVERT and subsequent monitoring of the patient.

With regards to **human experience of overdose** in the registration trials with CORVERT Injection, four patients were unintentionally overdosed. Based on known pharmacology, the clinical effects of an overdosage with ibutilide could exaggerate the expected prolongation of repolarization seen at usual clinical doses. Medical events (e.g., proarrhythmia, AV block) that occur after the overdosage should be treated with measures appropriate for that condition.

Important Safety Information

LIFE-THREATENING ARRHYTHMIAS—APPROPRIATE TREATMENT ENVIRONMENT

CORVERT® (ibutilide fumarate injection) 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. 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 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.

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

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, although change in QTc was dose dependent for ibutilide, there was no clear relationship between risk of serious proarrhythmia and dose, 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. CORVERT is not recommended in patients who have previously demonstrated polymorphic ventricular tachycardia (e.g., torsades de pointes).

During registration trials, 1.7% of patients with atrial flutter or atrial fibrillation treated with CORVERT developed sustained polymorphic ventricular tachycardia requiring cardioversion. In two cases, the VT degenerated into ventricular fibrillation, requiring immediate defibrillation. 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 overdrive cardiac pacing, electrical cardioversion, or defibrillation. Pharmacologic therapies include magnesium sulfate infusions. Treatment with antiarrhythmics should generally be avoided.

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 (H_1 receptor antagonists).

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.

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, calcium channel blockers, or beta-adrenergic blocking agents did not have effects on either the safety or efficacy of ibutilide in the clinical trials.

CORVERT should not be administered to a pregnant woman unless clinical benefit outweighs potential risk to the fetus.

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

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.

Clinical studies of ibutilide fumarate did not include sufficient numbers of subjects less than age 65 to determine whether they respond differently from older subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

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. Nonetheless, patients with abnormal liver function should be monitored by telemetry for more than the 4-hour period generally recommended. In clinical studies of 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.

In clinical trials of patients with atrial fibrillation or atrial flutter who received CORVERT in phase II/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%). Treatment-emergent medical events in these clinical trials with frequency of 2% and higher than that of placebo were ventricular extrasystoles (5.1%), nonsustained monomorphic ventricular tachycardia (4.9%), tachycardia/sinus tachycardia/supraventricular tachycardia (2.7%), and hypotension/postural hypotension (2.0%). In the post-cardiac surgery study, similar types of medical events were reported.

Indication

CORVERT is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification, 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.

CORVERT is for intravenous infusion only.

Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events in patients taking Corvert® to Pfizer at 1-800-438-1985. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

You may also contact our medical information department at 1-800-438-1985 if you have any questions about the information contained in this letter or the safe and effective use of Corvert®.

This letter is not intended as a complete description of the benefits and risks related to the use of Corvert®. Please see the Full Prescribing Information including BOXED WARNING at http://labeling.pfizer.com/showlabeling.aspx?id=673

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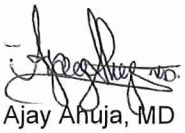
Sincerely,



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