PRODUCT MONOGRAPH

PrCORVERT®
(ibutilide fumarate injection)

0.1 mg/mL

Antiarrhythmic Agent

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ACTION AND CLINICAL PHARMACOLOGY

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

Ibutilide fumarate prolongs action potential duration in isolated adult cardiac myocytes and increases both atrial and ventricular refractoriness *in vivo*, i.e. class III electrophysiologic effects. Voltage clamp studies indicate that ibutilide at nanomolar concentrations, delays repolarisation 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 ibutilide in humans that are thought to be the basis for its antiarrhythmic effect.

PHARMACODYNAMICS

Electrophysiologic Effects: Ibutilide produces mild slowing of the sinus rate and atrioventricular conduction. Ibutilide produces no clinically significant effect on QRS duration at the recommended dosage. Ibutilide produces dose-related prolongation of the QT interval, which is thought to be associated with its antiarrhythmic activity. However, there is no established relationship between plasma concentration and antiarrhythmic activity. In studies in healthy volunteers, intravenous infusions of ibutilide resulted in prolongation of the QT interval that was directly correlated with ibutilide plasma concentration during and after 10-minute and 8-hour infusions. There is a steep relationship between plasma concentration of ibutilide and QT prolongation and the maximum effect on QT interval is a function of both the dose of ibutilide and the infusion rate. Prolongation in QT interval is similar in women and men.

Hemodynamic Effects: A study of hemodynamic function in patients stratified for ejection fractions (above or below 35%) demonstrated no clinically significant effects on cardiac output, mean pulmonary arterial pressure, or capillary wedge pressure at doses of ibutilide up to 0.03 mg/kg.

PHARMACOKINETICS

The pharmacokinetics of ibutilide in patients with atrial flutter or atrial fibrillation are similar regardless of the type of arrhythmia, age, sex, left ventricular ejection fraction, occurrence of polymorphic ventricular tachycardia, or the concomitant use of digoxin, calcium channel blockers, or beta-blockers.

Ibutilide pharmacokinetics is highly variable among subjects but it is linear with respect to the dose over a range of 0.01 mg/kg to 0.10 mg/kg.

After intravenous infusion, ibutilide plasma concentrations rapidly decrease in a tri-exponential fashion. It is cleared rapidly and highly distributed extravascularly as evidenced by the short distribution half-life and large volume of distribution. Drug distribution is one of the primary mechanisms responsible for termination of pharmacological effect. The initial distribution half-life is short (1.5 minutes) and the elimination half-life averages 6 hours (range from 2 to 12 hours). Ibutilide has a high systemic plasma clearance (approximately 29 mL/min/kg) that approximates liver blood flow. Total body clearance is primarily due to hepatic metabolism. It has a large steady-state volume of distribution (approximately 11 L/kg) and moderate degree of protein binding (approximately 40%).

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. Only the initial metabolite of the primary pathway (ω-oxidation) possesses class III electrophysiologic properties similar to ibutilide in an *in vitro* isolated rabbit myocardium model. Plasma concentrations of this metabolite are < 1% of the Cmax of ibutilide concentrations and, therefore, it is assumed not to contribute to overall pharmacologic effect.

In healthy male volunteers, about 82% of a 0.01 mg/kg dose of [^{14}C] ibutilide was excreted in the urine (about 7% of the dose as unchanged ibutilide) within 4 days of dosing, and the remainder (19%) was recovered in the faeces within 7 days of dosing.

The enantiomers of ibutilide have pharmacokinetic properties similar to each other and there is no evidence that one enantiomer is safer than the other or the racemate. Substantial racemization of one isomer to the other has not been observed.

INDICATIONS AND CLINICAL USE

No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

CORVERT (ibutilide fumarate injection) is indicated for the rapid conversion of atrial fibrillation or atrial flutter to sinus rhythm. CORVERT should be considered an alternative to electric cardioversion.

Patients with atrial arrhythmias of longer duration are less likely to respond to CORVERT. The effectiveness of CORVERT 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, but sometimes without documented QT prolongation. In placebo-controlled clinical studies, possibly causally related sustained polymorphic ventricular tachycardia, which required

cardioversion, occurred in 3.2% (7/218) of the patients with atrial flutter and 1.5% (4/340) of those with atrial fibrillation.

None of the patients who received placebo in the placebo-controlled clinical studies experienced sustained polymorphic ventricular tachycardia (*see* WARNINGS - Proarrhythmia, ADVERSE REACTIONS, and PHARMACOLOGY). 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 lasting more than 2 to 3 days must be adequately anticoagulated, generally for at least 2 weeks.

<u>Choice of Patients</u>

Patients with chronic atrial fibrillation have a strong tendency to revert after conversion to sinus rhythm, and treatments to maintain sinus rhythm carry risks.

Therefore, patients to be treated with CORVERT 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 such that CORVERT is likely to offer an advantage compared with alternative management.

CONTRAINDICATIONS

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

WARNINGS

Proarrhythmia

Like other antiarrhythmic agents, CORVERT (ibutilide fumarate injection) can induce or worsen ventricular arrhythmias, which, in some patients, might have potentially fatal consequences. Torsades de pointes, a polymorphic ventricular tachycardia (VT) that develops in the setting of QT interval prolongation, might occur because of the effect CORVERT has on cardiac repolarization. However, 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 this risk may be increased with bradycardia, a varying heart rate, or hypokalemia. In clinical trials, patients with atrial fibrillation or atrial flutter having QT_C interval >440 msec or serum potassium ≤4.0 mM/l were excluded. Although change in QT_C was directly related to ibutilide dosage, there was no clear relationship between risk of serious proarrhythmias and dose in clinical studies. This might have been due to the small number of events observed.

Because proarrhythmic events must be anticipated, CORVERT, as with other class III agents, is not recommended for patients with QTc intervals > 440 msec.

Before treatment with CORVERT, hypokalemia and hypomagnesemia should be corrected to reduce the potential for proarrhythmia. Patients should be closely monitored 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 VT includes discontinuation of CORVERT, correction of electrolyte abnormalities, (especially potassium and magnesium), and overdrive cardiac pacing, and electrical cardioversion or defibrillation. Pharmacologic therapies include magnesium sulfate infusions. Treatment of polymorphic VT with antiarrhythmics generally should be avoided.

During three placebo-controlled clinical trials involving patients treated with CORVERT (see ADVERSE REACTIONS, and PHARMACOLOGY - Placebo-Controlled Clinical Trials), 3.2% of 218 patients with atrial flutter and 1.2% of 340 patients with atrial fibrillation developed ibutilide-related sustained polymorphic VT requiring cardioversion; 7.8% of 218 patients with atrial flutter and 1.5% of 340 patients with atrial fibrillation experienced ibutilide-related nonsustained polymorphic VT. In the placebo-controlled clinical trial in post cardiac surgery patients, none of 77 patients with atrial flutter and 1.4% of 141 patients with atrial fibrillation experienced ibutilide-related sustained polymorphic VT; none of 141 patients with atrial flutter and 0.7% of 141 patients with atrial fibrillation experienced non-sustained polymorphic VT. In clinical trials, many initial episodes of polymorphic VT occurred during or soon after the infusion was stopped but generally within 40 minutes from the beginning of treatment. However, there were instances of recurrent polymorphic VT that occurred about 3 hours after the initial infusion of ibutilide.

Sustained monomorphic VT occurred in 0.2% of the patients, and nonsustained monomorphic VT occurred in 5.5% of patients in the four placebo-controlled studies. All patients with proarrhythmias in the controlled trials recovered with or without interventions. All patients with sustained VT received interventions, mainly DC shocks or intravenous magnesium sulfate.

Patients with a history of congestive heart failure (CHF) or low ejection fraction had a higher incidence of sustained polymorphic ventricular tachycardia (VT) than those without these underlying conditions (see PRECAUTIONS).

Skilled personnel and proper equipment, such as cardiac monitoring equipment, a cardioverter/defibrillator, intracardiac pacing facilities, and medication for treatment of sustained ventricular tachycardias, including polymorphic ventricular tachycardia, must be available during and after administration of CORVERT (see DOSAGE AND ADMINISTRATION).

Heart Block

Nine (1.5%) CORVERT-treated patients experienced reversible heart block: five had first degree, three had second degree and one had complete heart block.

PRECAUTIONS

Congestive Heart failure

CORVERT (ibutilide fumarate) caused a higher incidence of polymorphic VT in patients who had a history of congestive heart failure or low ejection fraction than those without these underlying conditions.

Torsade de Pointes

CORVERT is not recommended in patients with a history of polymorphic ventricular tachycardias (e.g., torsades de pointes).

Use in Patients with Hepatic Dysfunction

The safety, efficacy and pharmacokinetics of CORVERT have not been formally studied in patients with hepatic dysfunction. However, there are no changes in dosing recommendations for patients with hepatic dysfunction based on the following considerations:

1) CORVERT is indicated only for intravenous therapy of short duration (≤30 minutes). CORVERT is dosed to a known, well-defined pharmacologic action (termination of arrhythmia), the occurrence of specific adverse events or to a maximum of two 10-minute infusions (see DOSAGE AND ADMINISTRATION).
2) The hepatic metabolic clearance of ibutilide is perfusion-rate limited and independent of hepatic function, as measured by serum alanine aminotransferase and aspartate aminotransferase.
3) Drug distribution appears to be one of the primary mechanisms responsible for termination of the pharmacologic effect.

Nevertheless, patients with impaired hepatic function should be closely monitored for more than the 4-hour period generally recommended.

Use in Patients with Renal Dysfunction

The safety, efficacy and pharmacokinetics of CORVERT have not been formally studied in patients with renal dysfunction. However, it is unlikely that dosage adjustment would be necessary because less than 10% of the dose of CORVERT is excreted unchanged in the urine and the metabolites of CORVERT do not contribute to overall pharmacologic effect. In patients who were treated with CORVERT, the clearance of ibutilide was independent of renal function as measured by estimated creatinine clearance (from a range 21 to 140 mL/min). No dosing changes are recommended.

Use in Geriatrics

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. Therefore, no changes in dosage are recommended for the elderly.

Use in Pediatrics

Clinical trials with CORVERT did not include patients under the age of 18 years and, therefore, safety and effectiveness of CORVERT in pediatric patients have not been established.

Use in Pregnant Women

CORVERT was teratogenic and embryocidal in reproduction studies in rats at oral doses 16 times the recommended clinical dose when corrected for oral bioavailability. Therefore, the potential risk to the fetus must be considered when anticipating treatment of pregnant women or women of child-bearing potential.

Use in Nursing Women

The excretion of ibutilide into breast milk has not been studied; therefore, breast feeding is not recommended during therapy with CORVERT.

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, 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 20mg/kg/day. On a mg/m^2 basis, corrected

for 3% bioavailability, the highest dose tested was approximately four times the maximum recommended human dose.

Drug Interactions

No specific or formal drug interaction studies have been conducted.

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 or within 4 hours post-infusion because of their potential to prolong refractoriness. These antiarrhythmics may be administered 4 hours after the CORVERT dosing.

Drugs that Prolong the QT Interval: The potential for proarrhythmia may increase with the administration of CORVERT to patients who are being treated with drugs that prolong the QT interval. These include psychoactive drugs such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, and pimozide; antihistamine drugs (eg., terfenadine, astemizole); antimicrobials (eg., erythromycin particularly intravenously); antimalarials (eg., halofantrine); gastrointestinal prokinetic drugs (eg., cisapride).

Digoxin: Supraventricular arrhythmias might 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. Concomitant treatment with digoxin did not affect either serum digoxin levels or the pharmacokinetics of ibutilide in clinical trials.

Calcium Channel Blocking Agents: Concomitant treatment with calcium channel blocking agents did not affect the pharmacokinetics of ibutilide in clinical trials.

Beta Adrenergic Blocking Agents: Concomitant treatment with beta adrenergic blocking agents did not affect the pharmacokinetics of ibutilide in clinical trials.

ADVERSE REACTIONS

CORVERT (ibutilide fumarate injection) has been evaluated for safety in 1085 patients with atrial flutter or atrial fibrillation. Approximately half of these patients received two 10-minute infusions of ibutilide 1 mg at a 10-minute interval. Seven hundred and seventy six of these patients were treated with CORVERT in placebo-controlled trials (see PHARMACOLOGY - Clinical Trials). In these placebo-controlled studies, adverse events regardless of causality were reported in 319 of 776 (41.1%) of the ibutilide-treated patients compared to 76 of 254 (29.9%) of the patients on placebo (see the table just below). This difference is accounted mainly by the significantly greater incidence of cardiovascular adverse events observed in ibutilide-treated patients and the majority of cardiovascular adverse events were ventricular tachyarrhythmias. (See the table below).

In placebo-controlled studies, the rate of discontinuation of patients on ibutilide due to adverse events, regardless of causality was 5% (39 of 776 patients) compared to 0% (0 of 254 patients) on placebo.

The main reasons for premature discontinuation of CORVERT treatment were the emergence of ventricular extrasystoles (6 of 776 patients; 0.8%), non-sustained monomorphic ventricular tachycardia (7 of 776 patients; 0.9%), non-sustained polymorphic ventricular tachycardia (14 of

776 patients; 1.8%), sustained polymorphic ventricular tachycardia (7 of 776 patients; 0.9%) and QT segment prolongation (6 of 776 patients; 0.8%).

The following serious or severe adverse events that occurred in the placebo-controlled trials, for which a causal relationship with ibutilide could not be excluded, were: non-sustained polymorphic ventricular tachycardia (7 of 776 patients), sustained polymorphic ventricular tachycardia (14 of 776 patients), sustained monomorphic ventricular tachycardia (2 of 776 patients), supraventricular tachycardia (1 of 776 patients), heart arrest (3 of 776 patients), ventricular extrasystoles (1 of 776 patients), bigeminy (1 of 776 patients), cerebrovascular accident (3 of 776 patients), atrioventricular block (2 of 776 patients), hypotension (3 of 776 patients) and dizziness (1 of 776 patients).

In the placebo controlled trials, the most common adverse events with an incidence of ≧1%, but also with an incidence equal or greater than placebo, regardless of causal relationship to ibutilide, were:

ADVERSE EVENTS WITH AN INCIDENCE ≥1% AND ≥PLACEBO

ADVERSE EVENT	**PLACEBO** N = 254	**IBUTILIDE** N = 776
CARDIOVASCULAR		
Chest pain	1.2%	2.6%
Bradycardia	0.8%	1.4%
Extrasystoles, ventricular	0.8%	3.7%
Hypotension	0.8%	2.6%
Non-sustained monomorphic ventricular tachycardia	0.4%	3.4%

ADVERSE EVENT	PLACEBO N = 254	IBUTILIDE N = 776
Non-sustained polymorphic ventricular tachycardia	0.4%	3.5%
Sinus bradycardia	0.8%	1.2%
Sustained polymorphic ventricular tachycardia	-	1.8%
Heart Arrest	-	1.0%
OTHER BODY SYSTEMS		
Headache	3.1%	4.1%
Procedural non-surgical event	1.2%	1.9%
Nausea	3.1%	4.8%
Dizziness	1.6%	1.8%
Diarrhea	1.6%	1.8%

Proarrhythmias

Proarrhythmias causally related to CORVERT observed in the placebo-controlled trials in patients with atrial fibrillation (AFIB) and atrial flutter (AFL) are shown in the following two tables.

Percent and number of patients with proarrhythmias possibly causally related to ibutilide (n/N = number of patients with proarrhythmias over the total number of patients with AFIB or AFL) in three placebo-controlled trials (see PHARMACOLOGY - Clinical Trials)

	Patients with AFIB % (n/N)	Patients with AFL % (n/N)
All proarrhythmias*	14/340 (4.1%)	35/218 (16.0%)
Non-sustained and sustained polymorphic VT	9/340 (2.7%)	24/218 (11.0%)
Sustained polymorphic VT	4/340 (1.2%)	7/218 (3.2%)

* Include non-sustained and sustained monomorphic and polymorphic VT but not premature beats or couplets

Percent and number of patients with proarrhythmias possibly causally related to ibutilide (n/N = number of patients with proarrhythmias over the total number of patients with AFIB or AFL) in the placebo-controlled trial (#017) in patients with atrial fibrillation or flutter following coronary artery bypass graft or valvular surgery (see PHARMACOLOGY - Clinical Trials)

	Patients with AFIB % (n/N)	**Patients with AFL** % (n/N)
All proarrhythmias*	8/141 (5.7%)	0/77 (0%)
Non-sustained and sustained polymorphic VT	3/141 (2.1%)	0/77 (0%)
Sustained polymorphic VT	2/141 (1.4%)	0/77 (0%)

* Include non-sustained and sustained monomorphic and polymorphic VT but not premature beats or couplets

Other adverse events in the placebo-controlled trials not necessarily causally related to ibutilide with an incidence greater than placebo and between 0.3 to 1% are: ***(incidence ibutilide, incidence placebo)*** constipation (0.9%, 0.4%), urinary tract infection (0.9%, 0.8%), first degree AV block (0.9%, 0.4%), bundle branch block (0.9%, 0%), supraventricular tachycardia (0.8%, 0%), QT segment prolongation (0.8%, 0%), confusion (0.8%, 0.4%), hypertension (0.6%, 0%), nodal arrhythmia (0.6%, 0%), fatigue (0.5%, 0.4%), bigeminy (0.5%, 0%), leukocytosis (0.4%, 0%), leg cramps (0.4%, 0%), insomnia (0.4%, 0%), atrial fibrillation (0.4%, 0%), second degree AV block (0.4%, 0%), abdominal cramp (0.3%, 0%), asthenia (0.3%, 0%), arthralgia (0.3%, 0%), myalgia (0.3%, 0%), tremor (0.3%, 0%), pruritis (0.3%, 0%), abnormal vision (0.3%, 0%), precordial chest pain (0.3%, 0%), generalized edema (0.3%, 0%), trauma (0.3%, 0%), hematoma (0.3%, 0%), phlebitis (0.3%, 0%), acute kidney failure (0.3%, 0%), dysuria (0.3%, 0%), angina pectoris (0.3%, 0%), ventricular arrhythmia (0.3%, 0%).

Laboratory Abnormalities

The clinically relevant laboratory abnormalities observed in the placebo-controlled trials of CORVERT included elevated liver function tests (ALT, AST), elevated BUN, elevated creatine kinase, elevated creatinine, either elevated or low serum electrolytes (magnesium, sodium, potassium), low haemoglobin and abnormal platelet or white blood cell counts.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the clinical trials with CORVERT (ibutilide fumarate injection), four patients were unintentionally overdosed. The largest dose was 3.4 mg administered over 15 minutes. One patient developed increased ventricular ectopy and monomorphic ventricular tachycardia, another patient developed third degree A-V block and nonsustained polymorphic VT, and two patients had no medical event reports. Based on known pharmacology, the clinical effects of an overdosage with ibutilide could be an exaggeration of the expected prolongation of repolarization seen at usual clinical doses. Medical events (eg, proarrhythmia, A-V block) that occur after the overdosage should be treated with measures appropriate for that condition (see WARNINGS, proarrhythmia).

DOSAGE AND ADMINISTRATION

The recommended dose of ibutilide is outlined in the table below. Infusion of CORVERT (ibutilide fumarate injection) should be stopped as soon as the presenting arrhythmia is terminated, or if sustained or nonsustained ventricular tachycardia, or marked prolongation of QT or QTc occurs.

Recommended Dose of CORVERT

Patient Weight	Initial Intravenous Infusion (over 10 minutes)	Second Intravenous Infusion
≥60 kg	1.0 mg ibutilide fumarate (One 10-mL vial)	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.
<60 kg	0.01 mg/kg ibutilide fumarate (0.1 mL/kg)	

Recommended Dose of CORVERT in Post Cardiac Surgery Patients

Patient Weight	Initial Intravenous Infusion (over 10 minutes)	Second Intravenous Infusion
≥60 kg	0.5 mg ibutilide fumarate (5 mL of 0.1 mg/mL solution)	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.
<60 kg	0.005 mg/kg ibutilide fumarate (0.05 mL/kg)	

In a study in patients with atrial fibrillation or flutter after valvular or CABG surgery, 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 and did not induce serious proarrhythmias unlike two 10-minute infusions of 1mg.

More rapid infusion is not recommended. CORVERT may be administered undiluted or diluted (see **Dilution**).

Doses in addition to the second infusion are not recommended because of the risk of adverse events associated with QT interval prolongation.

If new arrhythmias develop or the original arrhythmia worsens during administration of CORVERT, the infusion should be stopped immediately.

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 or in patients with clinically manifest liver dysfunction. 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 (see WARNINGS - Proarrhythmia).

Dilution: CORVERT may be administered undiluted or diluted in 50 mL of diluent. CORVERT may be added to 0.9% Sodium Chloride or 5% Dextrose Injection before infusion. The contents of one 10 mL vial (0.1 mg/mL ibutilide fumarate) may be added to a 50 mL infusion bag to form an admixture of 0.017 mg/mL ibutilide fumarate. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Compatibility:

The following diluents are compatible with CORVERT:

5% Dextrose

0.9% Sodium Chloride

The following intravenous solution containers are compatible with admixtures of CORVERT:

polyvinyl chloride plastic bags

polyolefin bags.

Stability: Admixtures of CORVERT, with the compatible diluents, should be used immediately after mixing.

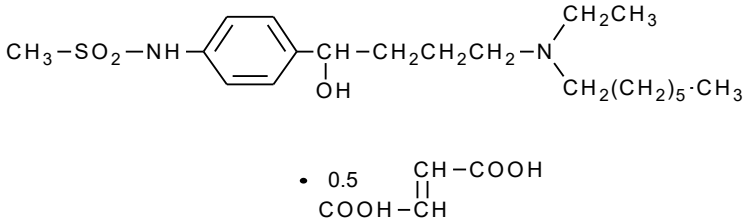
PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Ibutilide fumarate

Chemical Name: Methanesulfonamide, N-{4-{4-(ethylheptylamino)-1-hydroxybutyl}phenyl}, (+) (-), (E)-2-butenedioate (1:0.5) (hemifumarate salt)

Structural Formula



Molecular Formula: $C_{22}H_{38}N_2O_5S$

Molecular Weight: 442.62

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

Ibutilide fumarate (racemate) melts over the range of 117 to 121°C.

Ibutilide fumarate has one chiral centre, and exists as a racemate of the (+) and (-) enantiomers.

Composition

CORVERT (ibutilide fumarate) is an isotonic, clear, colourless, sterile aqueous solution. CORVERT contains 0.1 mg/mL ibutilide fumarate, which is equivalent to 0.087 mg/mL ibutilide (free base). Each mL of CORVERT contains the following excipients: sodium acetate trihydrate (0.189 mg), sodium chloride (8.90 mg), and sodium hydroxide solution or hydrochloric acid solution for pH adjustment to approximately 4.6, and water for injection.

Parenteral Products

Dilution: CORVERT may be administered undiluted or diluted in 50 mL of diluent. CORVERT may be added to 0.9% Sodium Chloride Injection or 5% Dextrose Injection before infusion. The contents of one 10 mL vial (0.1 mg/mL ibutilide fumarate) may be added to a 50 mL infusion bag to form an admixture of 0.017 mg/mL ibutilide fumarate.

Compatibility:

The following diluents are compatible with CORVERT:

5% Dextrose Injection

0.9% Sodium Chloride Injection.

The following intravenous solution containers are compatible with admixtures of CORVERT:

polyvinyl chloride plastic bags

polyolefin bags.

Stability: Admixtures of CORVERT, with the compatible diluents, should be used immediately after mixing.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration,

whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

Stability and Storage Recommendations

Store the product at controlled room temperature (15°C to 30°C). Keep the product in its original carton until used. Protect from light.

Admixtures of the product, with compatible diluents, should be used immediately after mixing. Protect from light.

AVAILABILITY OF DOSAGE FORMS

CORVERT (ibutilide fumarate injection) is supplied as an acetate-buffered isotonic solution adjusted to approximately pH 4.6 in a single use 10 mL clear glass vial with a pink flip-top.

CORVERT is supplied at a concentration of 0.1 mg/mL ibutilide fumarate.

PHARMACOLOGY

Preclinical Pharmacology

Ibutilide is a class III (Vaughan Williams classification) antiarrhythmic agent that prolongs the action potential duration of atrial and ventricular cardiac cells and tissue.

In vitro studies using concentrations of ibutilide with antiarrhythmic activity in canine models of atrial or ventricular arrhythmias (10^{-8}M to 10^{-7}M) have shown that ibutilide increases an inward, depolarizing sodium current, prolonging the duration of the action potential of atrial and ventricular myocytes. The net result on cardiac action potential duration is a dose-related increase in the duration of phase 2 and 3 of the intracellular potential and in refractoriness. Only at concentrations $\geq 10^{-6}$ M did ibutilide increase outward current carried primarily by potassium during action potential phase 3 or depressed upstroke velocity (sodium current, phase 0), and cardiac conduction occurred at a concentration of 10^{-5} M. In these studies, ibutilide did not show direct actions on cardiac contraction.

In vivo studies in various models of atrial arrhythmias, which are dependent upon reentrant cardiac conduction, established the efficacy of ibutilide. In all the animal studies, ibutilide produced significant class III effects, i.e, increased refractory periods, QT intervals, and/or duration of the monophasic action potential that correlated with its antiarrhythmic efficacy. Administration of ibutilide in the presence of nadolol or diltiazem did not reduce the class III electrophysiologic actions of ibutilide.

Clinical Pharmacology

Pharmacodynamics

Electrophysiologic Effects: Ibutilide caused a dose-related increase in the duration of the QT interval over a range of 0.001 to 0.03 mg/kg infused intravenously for 10 minutes. In healthy volunteers and patients with atrial flutter or fibrillation, QT prolongation was related to ibutilide plasma concentration. The maximum effect on QT was a function of both the dose and the rate of infusion. Ibutilide had no clinically significant effect on QRS duration, sinus rate and atrioventricular conduction. Changes observed usually returned to baseline within 2 to 4 hours. In patients scheduled for invasive electrophysiologic study, intravenous infusion of ibutilide at doses up to 0.03 mg/kg for 10 minutes followed by 0.006 mg/kg for 30 minutes were accompanied by significant dose-related increases in depolarization duration, and in atrial and ventricular refractory periods. Other changes, AV refractory period, A-H and H-V intervals, sinus node cycle length, atrial and ventricular stimulation threshold, and Wenkebach cycle length, when they occurred, were not clinically significant nor dose-related.

Hemodynamic Effects*:* Decreases in arterial blood pressure were not clinically significant for the great majority of patients with atrial flutter or fibrillation. A study of hemodynamic function in patients with ejection fraction both above and below 35% showed no clinically significant effects on cardiac output, mean pulmonary blood arterial and capillary wedge pressures at doses of ibutilide up to 0.03 mg/kg.

Pharmacokinetics in Subpopulations

Pediatric: Clinical trials with ibutilide in patients with atrial fibrillation and atrial flutter did not include anyone under the age of 18.

Geriatric: 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 with patients 65 years and older.

Gender: The pharmacokinetics of ibutilide in patients with atrial flutter or atrial fibrillation are similar in males and females.

Hepatic Insufficiency: A formal examination of the effect of hepatic impairment on the pharmacokinetics of ibutilide has not been done since the intrinsic clearance of ibutilide is high, potential first pass problems are circumvented because ibutilide is given intravenously, and there is possibly some extrahepatic elimination of ibutilide. Using Bayesian estimates and population kinetics, the effect of hepatic impairment on ibutilide pharmacokinetics was assessed. There was no apparent change in ibutilide clearance of in those patients with elevated ALT and AST. Severe hepatic impairment might be associated with decreased plasma albumin, which could affect distribution. However, since ibutilide is only 41% plasma protein bound, effects on ibutilide distribution would likely be minimal even in severe cases of hepatic failure.

Ibutilide dose does not need to be adjusted in patients with hepatic insufficiency (see PRECAUTIONS - Use in Patients with Hepatic Dysfunction).

Renal Insufficiency: A formal examination of the effect of renal impairment on the pharmacokinetics of ibutilide has not been done; however, a population kinetics approach was used to address that issue. No significant relationship was found, which is not surprising given that ibutilide is eliminated predominantly by metabolism. Less than 10% of the dose of CORVERT is excreted unchanged in the urine and the metabolites of CORVERT do not contribute to overall pharmacologic effect.

Changes in plasma protein concentrations secondary to renal failure will likely have minimal effects on the distribution of ibutilide. The dose of ibutilide does not need to be adjusted in patients with renal insufficiency (see PRECAUTIONS - Use in Patients with Renal Dysfunction).

Drug-Drug Interactions:

Since ibutilide is moderately plasma protein bound (41%), it is unlikely that any displacement interaction with a coadministered drug will significantly alter the distribution of ibutilide. In clinical studies of ibutilide, Vc and Vss remained constant despite the coadministration of digoxin, calcium channel blockers, and β-adrenergic blockers.

The major route of elimination of ibutilide is metabolism. It has been established that, if over 50% of a drug's elimination involves a single isozyme of the cytochrome P450 enzyme system, there is a potential for a drug-drug interaction if an inhibitor, co-substrate, or inducer of that particular isozyme is coadministered.

Since ibutilide is not metabolized primarily by a single isoform of cytochrome P450 commonly associated with drug elimination, and since ibutilide has a high intrinsic clearance, drug-drug interactions involving elimination of ibutilide will likely not be a problem.

Using a population pharmacokinetics approach, it was found that coadministration of calcium channel blockers, digoxin, and β-adrenergic blockers, which could be given concomitantly with ibutilide in the clinical setting, had no significant effect on the clearance of ibutilide.

Logistic regression analysis of data from a pivotal clinical trial of ibutilide showed that ibutilide did not affect the pharmacokinetics of coadministered drugs. In another clinical study of ibutilide, plasma concentrations of digoxin were found to be virtually the same before and after ibutilide treatment.

Clinical Trials

CORVERT (ibutilide fumarate injection) has been evaluated for efficacy and safety in four placebo-controlled clinical trials involving 1030 patients with atrial flutter or atrial fibrillation. In one of those four placebo-controlled clinical trials, the safety and efficacy of CORVERT for treating atrial flutter or atrial fibrillation in post cardiac surgery patients was assessed. Seven hundred and seventy six of these patients were treated with CORVERT in the four placebo-controlled trials. Approximately half of these patients received two 10-minute infusions of CORVERT 1 mg at a10-minute interval.

Placebo-controlled Studies of CORVERT in Non Post Cardiac Surgery Patients:

Three double-blinded, placebo-controlled studies, in which CORVERT was administered to patients with sustained atrial flutter (AFL) or atrial fibrillation (AFIB) ranging in duration from 3 hours to 90 days, were conducted. A total of 558 patients received CORVERT. One study was a dose-response study in which patients were randomized either to a single dose of placebo or 0.005 (41of 558 patients), 0.010 (40 of 558 patients), 0.015 (38 of 558 patients), or 0.025 (40 of 558 patients) mg/kg of CORVERT. In another study, patients were randomized to placebo, 1mg

of CORVERT followed by 0.5 mg (86 of 558 patients), or 1 mg of CORVERT followed by a second dose of 1mg (94 of 558 patients); patients <60 kg received 0.005 mg/kg and 0.01 mg/kg instead of 0.5 mg and 1 mg, respectively. In the remaining study, patients were randomized to placebo or two 1mg infusions (219 of 558 patients) of CORVERT. In all the studies, patients were stratified according to presenting arrhythmia.

The inclusion/exclusion criteria for enrolling patients were similar across the three placebo-controlled studies. Patients ranged in age from 18 to 80 years. Duration of atrial flutter/fibrillation was greater than 3 hours and up to 90 days. Patients in AFIB for more than 3 days were coagulated for at least 2 weeks before attempting conversion.

Patients were hemodynamically stable and were excluded for specific cardiovascular conditions such as symptomatic heart failure, acute myocardial infarction or cardiac surgery within three months of study entry, severe hypotension and unstable angina.

To avoid treating patients who might be predisposed to torsade de pointes, serum potassium concentrations had to be above 4.0 mEq/L before infusions were administered, patients could not be taking class I or III antiarrhythmics or other drugs known to increase the QT interval, or have a QT interval greater than 440 msec and pulse rate less than 60 beats/min. Electrical cardioversion was allowed 90 minutes post-infusion. Other antiarrhythmic drugs were allowed 4 hours post-infusion.

In all three studies, termination of arrhythmia was the primary efficacy endpoint. Patients were monitored for “success” or “failure” for one hour from the end of the last infusion.

Successes were defined as the termination of atrial fibrillation or flutter for any length of time within one hour following treatment.

Conversion of atrial flutter/fibrillation usually occurred within 30 minutes of the start of infusion and was dose-related. Patients were monitored for 24 hours, and most converted patients remained in normal sinus rhythm during that time (83-86%). Overall, results from the three placebo-controlled studies suggest that atrial flutter is terminated by CORVERT more effectively than atrial fibrillation. The rate of conversion from AFIB to sinus rhythm after the first dose of 1mg of ibutilide was 12% (30 of 245 patients) compared to 0% (0 of 69 patients) after the first dose of placebo and an additional 20% (37 of 185 patients) converted to sinus rhythm after the second 1mg dose of ibutilide compared to 1.4% (1 of 69 patients) after the second dose of placebo.

For patients with AFL, the rate of conversion after the first 1 mg dose of ibutilide was 24% (30 of 125 patients) compared to 0% (0 of 53 patients) after the first dose of placebo and an additional 54% (35 of 65 patients) converted after the second 1 mg dose of ibutilide compared to 1.9% (1 of 53 patients) after the second dose of placebo.

The incidence of treatment emergent adverse events in the three placebo-controlled studies of CORVERT in non post cardiac surgery patients was similar in the CORVERT and placebo treated patients except for cardiovascular medical events. The incidence of cardiovascular events was approximately 2.5 times greater in the CORVERT population than in the placebo treated population. The higher incidence of cardiovascular events in the CORVERT population is attributed to, in large part, the more frequent occurrence of proarrhythmias in the CORVERT population compared to the placebo treated population (see ADVERSE REACTIONS-adverse events and proarrhythmia tables).

Placebo-controlled Study of CORVERT in Post Cardiac Surgery Patients:

In a double-blind study which tested the efficacy of CORVERT on the termination of atrial flutter/fibrillation following coronary artery bypass grafting (CABG) or valvular surgery, 302 patients who had atrial fibrillation/flutter that occurred between 24 hours and 7 days after surgery and that had a duration between 1 hour and 3 days were enrolled.

They were randomised to receive two 10-minute infusions of the same dose with 10 minutes in between: placebo (84 patients), or 0.25mg (75 patients), 0.5mg (73 patients) or 1 mg (70 patients) ibutilide. Other eligibility criteria were similar to those listed above for the non post cardiac surgery patient as was the primary efficacy endpoint.

The overall success rates after the two-infusion regimen were as follows: placebo = 15%; 0.25 mg ibutilide = 40%; 0.5 mg ibutilide = 47%; and 1 mg ibutilide = 57%. Episodes of polymorphic VT occurred during or after the second infusion in 5 patients in the 1 mg group while none occurred in the 0.5 mg group. The incidence of proarrhythmia in post cardiac surgery patients is summarized in the following table.

Number and Percentage of Post Cardiac Surgery Patients Who Experienced Proarrhythmia

Arrhythmia	Placebo (N=84)	0.25 mg (N=75)	0.5 mg (N=73)	1 mg (N=70)	Total (N=302)
Sustained polymorphic VT	**0 (0%)**	**0 (0%)**	**0 (0%)**	**2 (2.9%)**	**2 (0.7%)**
Nonsustained polymorphic VT	**1 (1.2%)**	**0 (0%)**	**0 (0%)**	**3 (4.3%)**	**4 (1.3%)**
Nonsustained monomorphic VT	**1 (1.2%)**	**1 (1.3%)**	**3 (4.1%)**	**3 (4.3%)**	**7 (2.3%)**

Note: one patient in the 1 mg dose group reported both sustained and nonsustained polymorphic VT

Therefore, a 10-minute IV infusion of 0.5 mg of CORVERT followed by a second infusion of the same dose represents a safer and a clinically relevant dosing regimen in the post-cardiac surgery patient population.

TOXICOLOGY

Acute toxicity

Acute toxicity studies with ibutilide were conducted in mice, rats, and dogs. Ibutilide fumarate is moderately toxic, with an approximate intravenous single-dose median lethal dose between 50 and 100 mg/kg (greater than 1500 to 3000 times the maximum therapeutic dose for a 60-kg patient). In animals under visual observation only, signs of ibutilide toxicity were prostration, rapid, gasping breathing and convulsions.

Long-term toxicity

Intravenous administration:

Fourteen day intravenous studies in rats and in dogs demonstrated species differences: dogs developed toxicities (convulsions, degeneration/atrophy of testicular tissue) at doses an order of magnitude lower than the rat. There is no apparent explanation for the difference in species sensitivity. Differences in metabolism may contribute. Some inter-animal differences in clearance were also noted in the dog. The NOEL for definitive CNS effects was 2.5 mg/kg/day in dogs and 12.5 mg/kg/day in rats, and the exposures based on AUC were approximately 3-fold larger in the rat than in the dog at these dose levels.

Other salient signs of drug effect included mucification of the vaginal epithelium and proliferation of mammary glands with some evidence of secretory activity (25-50 mg/kg/day in rat), and increased heart weight (2.5 mg/kg/day in dog). The animal data indicate a safety margin of at least 75-fold when ibutilide is administered intravenously to humans.

Oral administration:

Species differences in toxicity also were noted between dogs and rats when ibutilide was administered orally. The most obvious difference was again the occurrence of CNS effects in dogs and lack thereof in rats. This difference was possibly due to the greater oral bioavailability in dogs (dogs: 18% to 84%, rats: 2.6% to 12.8%).

In a 2-week rat study, one of 15 rats had evidence of decreased grooming and vaginal mucification at the 16 mg/kg/day dose (close to no-effect dose), with testicular atrophy/degeneration and mammary gland proliferation occurring at higher (100 and 250 mg/kg/day, respectively) doses. In a 2-week dog study, doses of 12 mg/kg/day caused no notable effects while the 24 mg/kg/day dose produced apprehension, decreased activity, restlessness, aggression, body tremors, and convulsions.

Although the CNS signs occurred mainly on study Day 1 in dogs with some type of tolerance developing after that, the difference in the manifestation of toxic effects between the two species is noteworthy. Testicular degeneration was noted for 1 male dog and myocardial degeneration for 1 female dog at 24 mg/kg/day.

Disposition studies in rats and dogs administered ibutilide orally indicated highly variable bioavailability and metabolism, which may explain some differences in the occurrence of CNS effects at different dose levels.

Carcinogenicity

No long-term animal studies were conducted to determine the carcinogenic potential of ibutilide because of the short-term duration of human therapy, and the lack of mutagenicity in a standard battery of tests.

Mutagenicity

The mutagenic potential of ibutilide was studied in the *in vitro* Salmonella/microsome test (Ames Assay), mammalian cell mutation assay, unscheduled DNA syntheses (UDS) assay, and in the *in vivo* micronucleus test. All study results were negative, indicating that ibutilide fumarate is not genotoxic.

Reproduction and Teratology

No drug-related effects on fertility or mating were observed in a reproductive study in rats. Ibutilide was teratogenic and embryocidal to rats at an oral dose of 20 mg/kg/day, which is 606 times the maximum recommended human intravenous dose (16 times the maximum recommended dose when correcting for 2.6% oral bioavailability in rats). Teratogenicity in rats at this high dose level given over much of the gestation period is not directly applicable to the human given a much lower dose for very few hours. The no-observed-adverse-effect level (NOEL) for reproductive findings in rats was 5 mg/kg/day, or four times the maximum recommended therapeutic dose when correcting for 2.6% oral bioavailability in rats.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

CORVERT®
(ibutilide fumarate injection)

Read this carefully before you start taking **CORVERT** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CORVERT.**

CORVERT is intended for use only in patients with life-threatening irregular heartbeats (arrhythmias). Most anti-arrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increase of sudden death. Your doctor will tell you about the risk and benefits of anti-arrhythmic therapy.

What is CORVERT used for?

CORVERT is used to restore a normal heart rhythm in adults with certain types of abnormal heart rhythm (arrhythmias):

- atrial fibrillation or
- atrial flutter

It is unknown how safe or effective CORVERT is for use in children.

How does CORVERT work?

CORVERT works to restore a normal heart rhythm.

What are the ingredients in CORVERT?

Medicinal ingredients: Ibutilide fumarate

Non-medicinal ingredients: Sodium acetate trihydrate, sodium chloride, sodium hydroxide solution or hydrochloric acid solution (to adjust pH), and water for injection.

CORVERT comes in the following dosage forms:

Solution for injection: 0.1 mg / mL.

Do not use CORVERT if:

- you are allergic to any of the ingredients in CORVERT (see "**What are the ingredients in CORVERT?**" above).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CORVERT. Talk about any health conditions or problems you may have, including if you:

- have low levels of potassium.
- have low levels of magnesium.
- have problems with your liver.
- have problems with your kidneys.
- have other heart problems.
- took a heart rhythm medication within 4 hours before you are going to be given CORVERT.

Other warnings you should know about:

Pregnancy, breastfeeding and women of childbearing age: You should not take CORVERT if you are:

- pregnant or planning to become pregnant. Your doctor will decide whether the benefit of giving you CORVERT outweighs the risk to your unborn baby. Tell your doctor if you become pregnant.
- breastfeeding or planning to breastfeed. CORVERT can pass into your breast milk.
- of childbearing age and are not using an effective and reliable method of birth control.

Laboratory Tests: CORVERT can cause abnormal blood test results for:

- Liver function tests
- Blood, Urea and Nitrogen (BUN) test
- Kidney function tests
- Tests to measure blood magnesium, potassium and sodium levels
- Tests to measure hemoglobin, platelets and white blood cell counts

Your doctor will decide when to perform blood tests and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CORVERT:

- Other drugs used to treat abnormal heart rhythms, such as:
    - disopyramide,
    - quinidine,
    - procainamide,
    - amiodarone,
    - sotalol

- Drugs that prolong the QT interval. These include:
    - Psychoactive drugs, such as:
        - Phenothiazines
        - Tricyclic antidepressants

    - Tetracyclic antidepressants
    - Pimozide
- Drugs used to treat allergies (antihistamines) such as terfenadine and astemizole
- Drugs used to treat infections, particularly when erythromycin given through your vein (intravenously)
- Drugs to treat malaria (antimalarial) such as halofantrine
- Drugs used to treat gastrointestinal problems such as cisapride.

How CORVERT is given:
CORVERT will always be given to you:

- by a doctor or nurse
- as an injection into your vein as an infusion (intravenous infusion)
- in a place where there is continuous ECG monitoring and the proper equipment available to the doctor or nurse during and after treatment with CORVERT.

Usual dose:
Your doctor will determine the right dose of CORVERT for you based on your weight.

Overdose:

If you think you have been given too much CORVERT, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using CORVERT?

These are not all the possible side effects you may feel when taking CORVERT. You will be watched closely to check for serious side effects. Tell your caregiver if you feel short of breath or like you might pass out. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- slow heart beat
- high blood pressure
- headache
- constipation
- bladder infection
- fatigue
- increase in white blood cells
- leg cramps
- difficulty sleeping
- weakness
- lack of energy
- joint pain
- muscle pain
- itching

- swelling
- bruising
- inflammation of the veins
- difficulty urinating
- nausea
- vomiting
- diarrhea
- confusion
- trouble with your vision

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Allergic reaction: hives; difficulty breathing; swelling of face, lips, tongue, or throat			√
Chest pain, palpitations, irregular heartbeat		√	
Low blood pressure: fainting, dizziness			√
Tremor/abnormal involuntary movements			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

CORVERT will be stored by your healthcare professional.

Store:

- At room temperature (15 -30°C).
- In its original carton until it is used to protect it from light.

Keep out of reach and sight of children.

If you want more information about CORVERT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (http://www.pfizer.ca), Pfizer Canada ULC at 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC

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