

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CORLANOR safely and effectively. See full prescribing information for CORLANOR.

CORLANOR® (ivabradine) tablets, for oral use
CORLANOR® (ivabradine) oral solution
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated:

- To reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with reduced left ventricular ejection fraction. (1.1)
- For the treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients ages 6 months and older. (1.2)

DOSAGE AND ADMINISTRATION

Adult and pediatric patients greater than 40 kg

- Starting dose is 2.5 (pediatrics and vulnerable adults) or 5 mg twice daily with food. After 2 weeks of treatment, adjust dose based on heart rate. The maximum dose is 7.5 mg twice daily. (2.1)

Pediatric patients less than 40 kg

- Starting dose is 0.05 mg/kg twice daily with food. Adjust dose at two-week intervals by 0.05 mg/kg based on heart rate. Maximum dose is 0.2 mg/kg (patients 6 months to less than 1 year old) or 0.3 mg/kg (patients 1 year old and older), up to a total of 7.5 mg twice daily.

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg, 7.5 mg (3)
- Oral Solution: 5 mg/5 mL (1 mg/mL) (3)

CONTRAINDICATIONS

- Acute decompensated heart failure (4)
- Clinically significant hypotension (4)
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present (4)
- Clinically significant bradycardia (4)
- Severe hepatic impairment (4)
- Heart rate maintained exclusively by the pacemaker (4)
- In combination with strong cytochrome CYP3A4 inhibitors (4)

WARNINGS AND PRECAUTIONS

- Fetal toxicity: Females should use effective contraception. (5.1)
- Monitor patients for atrial fibrillation. (5.2)
- Monitor heart rate decreases and bradycardia symptoms during treatment. (5.3)
- Not recommended in patients with 2nd degree AV block. (5.3)

ADVERSE REACTIONS

Most common adverse reactions occurring in $\geq 1\%$ of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-772-6436 (1-800-77-AMGEN) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid CYP3A4 inhibitors or inducers. (7.1)
- Negative chronotropes increase risk of bradycardia; monitor heart rate. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Heart Failure in Adult Patients

Corlanor is indicated to reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction $\leq 35\%$, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

1.2 Heart Failure in Pediatric Patients

Corlanor is indicated for the treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in pediatric patients aged 6 months and older, who are in sinus rhythm with an elevated heart rate.

2. DOSAGE AND ADMINISTRATION

2.1 Adults

The recommended starting dose of Corlanor is 5 mg twice daily with food. Assess patient after two weeks and adjust dose to achieve a resting heart rate between 50 and 60 beats per minute (bpm) as shown in Table 1. Thereafter, adjust dose as needed based on resting heart rate and tolerability. The maximum dose is 7.5 mg twice daily. In adult patients unable to swallow tablets, Corlanor oral solution can be used [*see Clinical Pharmacology (12.3)*].

In patients with a history of conduction defects or other patients in whom bradycardia could lead to hemodynamic compromise, initiate therapy at 2.5 mg twice daily before increasing the dose based on heart rate [*see Warnings and Precautions (5.3)*].

Table 1. Dose Adjustment for Adults

Heart Rate	Dose Adjustment
> 60 bpm	Increase dose by 2.5 mg (given twice daily) up to a maximum dose of 7.5 mg twice daily
50-60 bpm	Maintain dose
< 50 bpm or signs and symptoms of bradycardia	Decrease dose by 2.5 mg (given twice daily); if current dose is 2.5 mg twice daily, discontinue therapy*

*[*see Warnings and Precautions (5.3)*]

2.2 Pediatric Patients

Recommended Dosage

Pediatric Patients 6 Months of Age and Older Weighing Less than 40 kg (Oral Solution)

The recommended starting dose of Corlanor oral solution in pediatric patients 6 months of age and older and weighing less than 40 kg is 0.05 mg/kg twice daily with food. Assess patient at two-week intervals and adjust dose by 0.05 mg/kg to target a heart rate (HR) reduction of at least 20%, based on tolerability. The maximum dose is 0.2 mg/kg twice daily for patients 6 months to less than 1 year old, and 0.3 mg/kg twice daily for patients 1 year old and older, up to a total of 7.5 mg twice daily.

If a dose of Corlanor is missed or spit out, do not give another dose to make up for the missed or spit out dose. Give the next dose at the usual time.

Pediatric Patients Weighing 40 kg and Greater (Tablets)

The recommended starting dose of Corlanor tablets in pediatric patients weighing more than 40 kg is 2.5 mg twice daily with food. Assess patient at two-week intervals and adjust dose by 2.5 mg to target a heart rate (HR) reduction of at least 20%, based on tolerability. The maximum dose is 7.5 mg twice daily. In patients unable to swallow tablets, Corlanor oral solution can be used.

Dose Reduction for Bradycardia

If bradycardia develops, reduce the dose to the previous titration step. In patients who develop bradycardia at the recommended initial dosage, consider reducing the dosage to 0.02 mg/kg twice daily.

Oral Solution Preparation and Administration

To administer Corlanor oral solution, empty the entire contents of the ampule(s) into a medication cup. With a calibrated oral syringe, measure the prescribed dose of Corlanor from the medication cup and administer the drug orally.

Corlanor oral solution is sterile and preservative-free. Discard the unused oral solution. Do not store or reuse any oral solution left in either the medication cup or an ampule.

3. DOSAGE FORMS AND STRENGTHS

Corlanor Tablets

5 mg: salmon-colored, oval-shaped, film-coated tablet, functionally scored on both edges, debossed with “5” on one face and bisected on the other face. The tablet is scored and can be divided into equal halves to provide a 2.5 mg dose.

7.5 mg: salmon-colored, triangular-shaped, film-coated tablet debossed with “7.5” on one face and plain on the other face.

Corlanor Oral Solution

Corlanor 5 mg/5 mL (1 mg/mL) oral solution is a colorless liquid in an opaque, plastic, ampule containing 5 mg of Corlanor in 5 mL of liquid.

4. CONTRAINDICATIONS

Corlanor is contraindicated in patients with:

- Acute decompensated heart failure
- Clinically significant hypotension
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
- Clinically significant bradycardia [*see Warnings and Precautions (5.3)*]
- Severe hepatic impairment [*see Use in Specific Populations (8.6)*]
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker) [*see Drug Interactions (7.3)*]
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors [*see Drug Interactions (7.1)*]

5. WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Corlanor may cause fetal toxicity when administered to a pregnant woman based on findings in animal studies. Embryo-fetal toxicity and cardiac teratogenic effects were observed in fetuses of pregnant rats treated during organogenesis at exposures 1 to 3 times the human exposures (AUC_{0-24hr}) at the maximum recommended human dose (MRHD) [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception when taking Corlanor [*see Use in Specific Populations (8.3)*].

5.2 Atrial Fibrillation

Corlanor increases the risk of atrial fibrillation. In the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT), the rate of atrial fibrillation was 5.0% per patient-year in patients treated with Corlanor and 3.9% per patient-year in patients treated with placebo [*see Clinical Studies (14)*]. Regularly monitor cardiac rhythm. Discontinue Corlanor if atrial fibrillation develops.

5.3 Bradycardia and Conduction Disturbances

Adult Patients

Bradycardia, sinus arrest, and heart block have occurred with Corlanor. The rate of bradycardia was 6.0% per patient-year in patients treated with Corlanor (2.7% symptomatic; 3.4% asymptomatic) and 1.3% per patient-year in patients treated with placebo. Risk factors for bradycardia include sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree atrioventricular block, bundle branch block), ventricular dyssynchrony, and use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, amiodarone). Bradycardia may increase the risk of QT prolongation which may lead to severe ventricular arrhythmias, including torsade de pointes, especially in patients with risk factors such as use of QTc prolonging drugs [see *Adverse Reactions* (6.2)].

Concurrent use of verapamil or diltiazem will increase Corlanor exposure, may themselves contribute to heart rate lowering, and should be avoided [see *Clinical Pharmacology* (12.3)]. Avoid use of Corlanor in patients with 2nd degree atrioventricular block unless a functioning demand pacemaker is present [see *Contraindications* (4)].

Pediatric Patients

Bradycardia and first-degree heart block were observed in pediatric patients treated with Corlanor. Asymptomatic and symptomatic bradycardia were observed in 6.8% and 4.1% of pediatric patients treated with Corlanor, respectively. In the placebo treatment arm, 2.4% of pediatric patients had asymptomatic bradycardia, but none had symptomatic bradycardia. Bradycardia was managed through dose titration but did not result in study drug discontinuation [see *Dosage and Administration* (2.2)].

6. ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Atrial Fibrillation [see *Warnings and Precautions* (5.2)]
- Bradycardia and Conduction Disturbances [see *Warnings and Precautions* (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Patients with Heart Failure

In SHIFT, safety was evaluated in 3,260 patients treated with Corlanor and 3,278 patients given placebo. The median duration of Corlanor exposure was 21.5 months.

The most common adverse drug reactions in the SHIFT trial are shown in Table 2 [see Warnings and Precautions (5.2), (5.3)].

Table 2. Adverse Drug Reactions with Rates \geq 1.0% Higher on Ivabradine than Placebo occurring in $>$ 1% on Ivabradine in SHIFT

	Ivabradine N = 3,260	Placebo N = 3,278
Bradycardia	10%	2.2%
Hypertension, blood pressure increased	8.9%	7.8%
Atrial fibrillation	8.3%	6.6%
Phosphenes, visual brightness	2.8%	0.5%

Luminous Phenomena (Phosphenes)

Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency). Phosphenes are usually triggered by sudden variations in light intensity. Corlanor can cause phosphenes, thought to be mediated through Corlanor's effects on retinal photoreceptors [see Clinical Pharmacology (12.1)]. Onset is generally within the first 2 months of treatment, after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity and led to treatment discontinuation in $<$ 1% of patients; most resolved during or after treatment.

Pediatric Patients with Heart Failure

The safety of Corlanor in pediatric patients 6 months to less than 18 years of age is based on a clinical trial [see Clinical Studies (14.2)] in symptomatic heart failure patients with dilated cardiomyopathy and elevated heart rate. This trial provides experience in 73 patients treated with Corlanor for a median duration of 397 days, and 42 patients given placebo. Bradycardia (symptomatic and asymptomatic) occurred at rates similar to those in adults. Phosphenes were observed in pediatric patients treated with Corlanor.

6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

The following adverse reactions have been identified in adults during post-approval use of Corlanor: syncope, hypotension, torsade de pointes, ventricular fibrillation, ventricular tachycardia, angioedema, erythema, rash, pruritus, urticaria, vertigo, and diplopia, and visual impairment.

7. DRUG INTERACTIONS

7.1 Cytochrome P450-Based Interactions

Corlanor is primarily metabolized by CYP3A4. Concomitant use of CYP3A4 inhibitors increases ivabradine plasma concentrations and use of CYP3A4 inducers decreases them. Increased plasma concentrations may exacerbate bradycardia and conduction disturbances.

The concomitant use of strong CYP3A4 inhibitors is contraindicated [*see Contraindications (4) and Clinical Pharmacology (12.3)*]. Examples of strong CYP3A4 inhibitors include azole antifungals (e.g., itraconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), HIV protease inhibitors (e.g., nelfinavir), and nefazodone.

Avoid concomitant use of moderate CYP3A4 inhibitors when using Corlanor. Examples of moderate CYP3A4 inhibitors include diltiazem, verapamil, and grapefruit juice [*see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

Avoid concomitant use of CYP3A4 inducers when using Corlanor. Examples of CYP3A4 inducers include St. John's wort, rifampicin, barbiturates, and phenytoin [*see Clinical Pharmacology (12.3)*].

7.2 Negative Chronotropes

Most patients receiving Corlanor will also be treated with a beta-blocker. The risk of bradycardia increases with concomitant administration of drugs that slow heart rate (e.g., digoxin, amiodarone, beta-blockers). Monitor heart rate in patients taking Corlanor with other negative chronotropes.

7.3 Pacemakers in Adults

Corlanor dosing is based on heart rate reduction, targeting a heart rate of 50 to 60 beats per minute in adults [*see Dosage and Administration (2.1)*]. Patients with demand pacemakers set to a rate ≥ 60 beats per minute cannot achieve a target heart rate < 60 beats per minute, and these patients were excluded from

clinical trials [see *Clinical Studies (14.1)*]. The use of Corlanor is not recommended in patients with demand pacemakers set to rates ≥ 60 beats per minute.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, Corlanor may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Corlanor in pregnant women to inform any drug-associated risks. In animal reproduction studies, oral administration of ivabradine to pregnant rats during organogenesis at a dosage providing 1 to 3 times the human exposure (AUC_{0-24hr}) at the MRHD resulted in embryo-fetal toxicity and teratogenicity manifested as abnormal shape of the heart, interventricular septal defect, and complex anomalies of primary arteries. Increased post-natal mortality was associated with these teratogenic effects in rats. In pregnant rabbits, increased post-implantation loss was noted at an exposure (AUC_{0-24hr}) 5 times the human exposure at the MRHD. Lower doses were not tested in rabbits. The background risk of major birth defects for the indicated population is unknown. The estimated background risk of major birth defects in the U.S. general population is 2 to 4%, however, and the estimated risk of miscarriage is 15 to 20% in clinically recognized pregnancies. Advise a pregnant woman of the potential risk to the fetus.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk

Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Pregnant patients with left ventricular ejection fraction less than 35% on maximally tolerated doses of beta-blockers may be particularly heart rate dependent for augmenting cardiac output. Therefore, pregnant patients who are started on Corlanor, especially during the first trimester, should be followed closely for destabilization of their congestive heart failure that could result from heart rate slowing.

Monitor pregnant women with chronic heart failure in 3rd trimester of pregnancy for preterm birth.

Data

Animal Data

In pregnant rats, oral administration of ivabradine during the period of organogenesis (gestation day 6-15) at doses of 2.3, 4.6, 9.3, or 19 mg/kg/day resulted in fetal toxicity and teratogenic effects. Increased

intrauterine and post-natal mortality and cardiac malformations were observed at doses ≥ 2.3 mg/kg/day (equivalent to the human exposure at the MRHD based on AUC_{0-24hr}). Teratogenic effects including interventricular septal defect and complex anomalies of major arteries were observed at doses ≥ 4.6 mg/kg/day (approximately 3 times the human exposure at the MRHD based on AUC_{0-24hr}).

In pregnant rabbits, oral administration of ivabradine during the period of organogenesis (gestation day 6-18) at doses of 7, 14, or 28 mg/kg/day resulted in fetal toxicity and teratogenicity. Treatment with all doses ≥ 7 mg/kg/day (equivalent to the human exposure at the MRHD based on AUC_{0-24hr}) caused an increase in post-implantation loss. At the high dose of 28 mg/kg/day (approximately 15 times the human exposure at the MRHD based on AUC_{0-24hr}), reduced fetal and placental weights were observed, and evidence of teratogenicity (ectrodactylia observed in 2 of 148 fetuses from 2 of 18 litters) was demonstrated.

In the pre- and post-natal study, pregnant rats received oral administration of ivabradine at doses of 2.5, 7, or 20 mg/kg/day from gestation day 6 to lactation day 20. Increased post-natal mortality associated with cardiac teratogenic findings was observed in the F1 pups delivered by dams treated at the high dose (approximately 15 times the human exposure at the MRHD based on AUC_{0-24hr}).

8.2 Lactation

Risk Summary

There is no information regarding the presence of ivabradine in human milk, the effects of ivabradine on the breastfed infant, or the effects of the drug on milk production. Animal studies have shown, however, that ivabradine is present in rat milk [*see Data*]. Because of the potential risk to breastfed infants from exposure to Corlanor, breastfeeding is not recommended.

Data

Lactating rats received daily oral doses of [^{14}C]-ivabradine (7 mg/kg) on post-parturition days 10 to 14; milk and maternal plasma were collected at 0.5 and 2.5 hours post-dose on day 14. The ratios of total radioactivity associated with [^{14}C]-ivabradine or its metabolites in milk vs. plasma were 1.5 and 1.8, respectively, indicating that ivabradine is transferred to milk after oral administration.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Corlanor may cause fetal harm, based on animal data. Advise females of reproductive potential to use effective contraception during Corlanor treatment [*see Use in Specific Populations (8.1)*].

8.4 Pediatric Use

The safety and effectiveness of Corlanor have been established in pediatric patients (age 6 months to less than 18 years old) and are supported by pharmacokinetic and pharmacodynamic trials and evidence from adequate and well-controlled trials of Corlanor in adult patients. The pediatric study included 116 patients in the following age groups: 17 patients in the 6 months to less than 12 months age group, 36 patients in the 1 year to less than 3 years age group, and 63 patients in the 3 years to less than 18 years age group [*see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)*].

The safety and efficacy of Corlanor have not been established in patients less than 6 months of age.

Animal Data

Ivabradine given orally to juvenile rats from post-natal day (PND) 7 until PND 77 at 7.5, 15 and 30 mg/kg/day did not affect post-natal (pre-weaning) development and reproductive performance (post-weaning development). Similar to adult animals, ivabradine decreased heart rate dose-dependently, and increased heart weights at the highest dose administered. Ivabradine also decreased white blood cell counts (lymphocytes) at the highest dose administered. The decrease in white blood cell counts partially reversed within a 3-week recovery period. Exposures in male and female rats at the No Observed Adverse Effect Level (NOAEL) of 7.5 mg/kg/day, was approximately 3 and 8 times, respectively, steady state exposure associated with the highest received maintenance doses across age groups in pediatric patients (based on AUCs).

8.5 Geriatric Use

No pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population. However, Corlanor has only been studied in a limited number of patients ≥ 75 years of age.

8.6 Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. Corlanor is contraindicated in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this population and an increase in systemic exposure is anticipated [see *Contraindications (4) and Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dosage adjustment is required for patients with creatinine clearance 15 to 60 mL/min. No data are available for patients with creatinine clearance below 15 mL/min [see *Clinical Pharmacology (12.3)*].

10. OVERDOSAGE

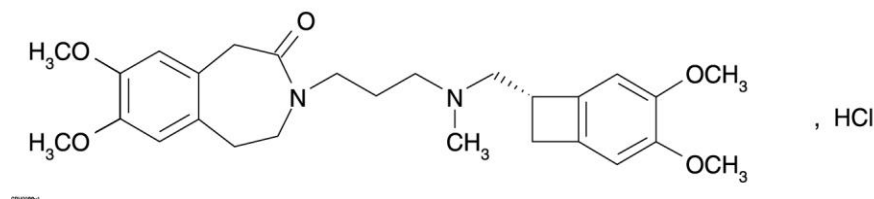
Overdose may lead to severe and prolonged bradycardia. In the event of bradycardia with poor hemodynamic tolerance, temporary cardiac pacing may be required. Supportive treatment, including intravenous (IV) fluids, atropine, and intravenous beta-stimulating agents such as isoproterenol, may be considered.

11. DESCRIPTION

Corlanor (ivabradine) tablets and oral solution contains ivabradine as the active pharmaceutical ingredient. Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f current, resulting in heart rate reduction with no effect on ventricular repolarization and no effects on myocardial contractility.

The chemical name for ivabradine hydrochloride is 3-(3-{[(*7S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl] methyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one, hydrochloride. The molecular formula is $C_{27}H_{36}N_2O_5 \cdot HCl$, and the molecular weight (free base + HCl) is 505.1 (468.6 + 36.5). The chemical structure of ivabradine is shown in Figure 1.

Figure 1. Chemical Structure of Ivabradine



Tablets

Corlanor tablets are supplied in 5 mg and 7.5 mg tablets for oral administration. The tablets contain 5 mg and 7.5 mg of ivabradine, as the active ingredient, equivalent to 5.39 mg and 8.09 mg of ivabradine hydrochloride, respectively. The tablets contain the following inactive ingredients: colloidal silicon dioxide, glycerol, hypromellose, lactose monohydrate, magnesium stearate, maize starch, maltodextrin, polyethylene glycol 6000, red iron oxide, titanium dioxide, and yellow iron oxide.

Oral Solution

Corlanor 5 mg/5 mL (1 mg/mL) oral solution is formulated as a sterile, preservative-free, colorless solution for oral administration. Each 5 mL ampule contains 5 mg of ivabradine, equivalent to 5.39 mg ivabradine hydrochloride, as the active ingredient. The solution contains the following inactive ingredients: maltitol and water.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corlanor blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I_f current, which regulates heart rate. In clinical electrophysiology studies, the cardiac effects were most pronounced in the sinoatrial (SA) node, but prolongation of the AH interval has occurred as has PR interval prolongation. There was no effect on ventricular repolarization and no effects on myocardial contractility [*see Clinical Pharmacology (12.2)*].

Corlanor can also inhibit the retinal current I_h . I_h is involved in curtailing retinal responses to bright light stimuli. Under triggering circumstances (e.g., rapid changes in luminosity), partial inhibition of I_h by Corlanor may underlie the luminous phenomena experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field [*see Adverse Reactions (6.1)*].

12.2 Pharmacodynamics

Corlanor causes a dose-dependent reduction in heart rate. The size of the effect is dependent on the baseline heart rate (i.e., greater heart rate reduction occurs in patients with higher baseline heart rate). At recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. Analysis of heart rate reduction vs. dose indicates a plateau effect at doses > 20 mg twice daily. In a study of patients with preexisting conduction system disease (first- or second-degree AV block or left or right bundle branch block) requiring electrophysiologic study, IV ivabradine (0.20 mg/kg) administration slowed the

overall heart rate by approximately 15 bpm, increased the PR interval (29 msec), and increased the AH interval (27 msec).

Corlanor does not have negative inotropic effects. Ivabradine increases the uncorrected QT interval with heart rate slowing but does not cause rate-corrected prolongation of QT.

12.3 Pharmacokinetics

The peak concentration (C_{max}) and area under the plasma concentration time curve (AUC) are similar for ivabradine and S 18982 between oral solution and tablets for the same dose.

Absorption and Bioavailability

Following oral administration, peak plasma ivabradine concentrations are reached in approximately 1 hour under fasting conditions. The absolute oral bioavailability of ivabradine is approximately 40% because of first-pass elimination in the gut and liver.

Food delays absorption by approximately 1 hour and increases plasma exposure by 20% to 40%. Corlanor should be taken with food [*see Dosage and Administration (2)*].

Ivabradine is approximately 70% plasma protein bound, and the volume of distribution at steady state is approximately 100 L.

Metabolism and Excretion

The pharmacokinetics of ivabradine are linear over an oral dose range of 0.5 mg to 24 mg. Ivabradine is extensively metabolized in the liver and intestines by CYP3A4-mediated oxidation. The major metabolite is the N-desmethylated derivative (S 18982), which is equipotent to ivabradine and circulates at concentrations approximately 40% that of ivabradine. The N-desmethylated derivative is also metabolized by CYP3A4. Ivabradine plasma levels decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours.

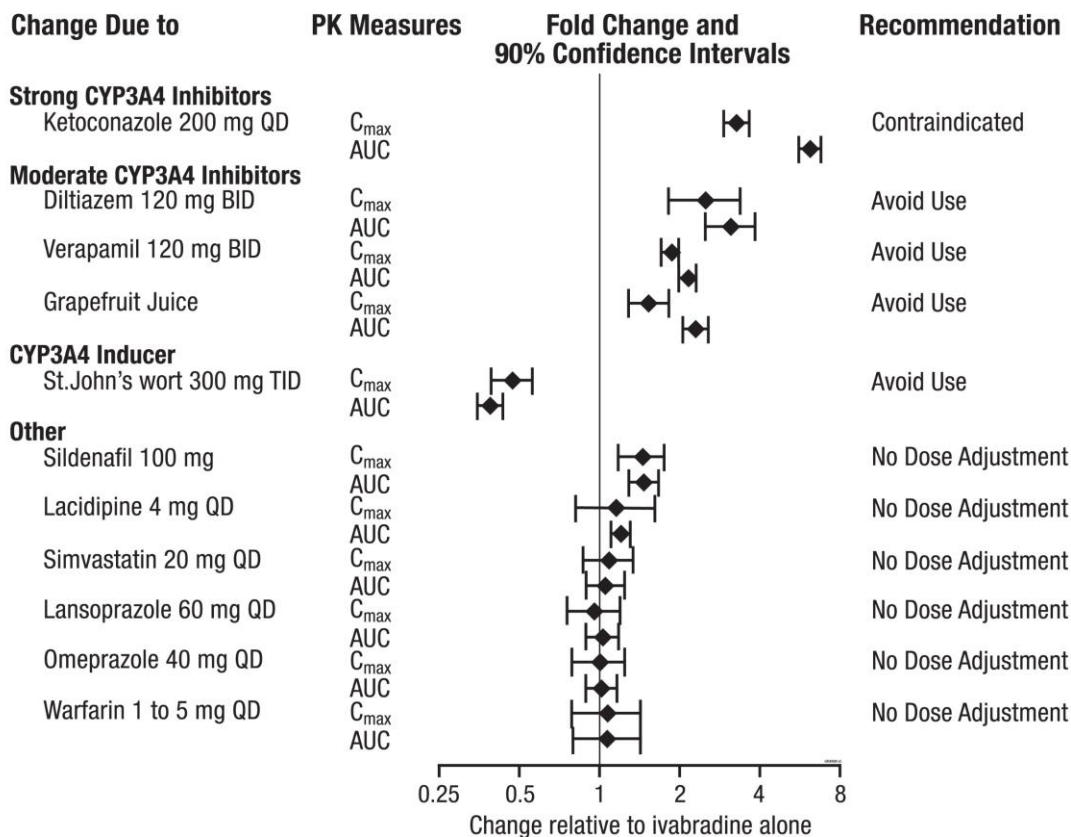
The total clearance of ivabradine is 24 L/h, and renal clearance is approximately 4.2 L/h, with ~ 4% of an oral dose excreted unchanged in urine. The excretion of metabolites occurs to a similar extent via feces and urine.

Drug Interactions

The effects of coadministered drugs (CYP3A4 inhibitors, substrates, inducers, and other concomitantly administered drugs) on the pharmacokinetics of Corlanor were studied in several single- and

multiple-dose studies. Pharmacokinetic measures indicating the magnitude of these interactions are presented in Figure 2.

Figure 2. Impact of Coadministered Drugs on the Pharmacokinetics of Corlanor



Digoxin exposure did not change when concomitantly administered with ivabradine. No dose adjustment is required when ivabradine is concomitantly administered with digoxin.

Effect of Ivabradine on Metformin Pharmacokinetics

Ivabradine, dosed at 10 mg twice daily to steady state, did not affect the pharmacokinetics of metformin (an organic cation transporter [OCT2] sensitive substrate). The geometric mean (90% confidence interval [CI]) ratios of C_{max} and AUC_{inf} of metformin, with and without ivabradine were 0.98 [0.83-1.15] and 1.02 [0.86-1.22], respectively. No dose adjustment is required for metformin when administered with Corlanor.

Specific Populations

Age

No pharmacokinetic differences (AUC or C_{max}) have been observed between elderly (≥ 65 years) or very elderly (≥ 75 years) patients and the overall patient population [see *Use in Specific Populations* (8.5)].

Hepatic Impairment

In patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of Corlanor were similar to that in patients with normal hepatic function. No data are available in patients with severe hepatic impairment (Child-Pugh C) [see *Contraindications* (4)].

Renal Impairment

Renal impairment (creatinine clearance from 15 to 60 mL/min) has minimal effect on the pharmacokinetics of Corlanor. No data are available for patients with creatinine clearance below 15 mL/min.

Pediatrics

The pharmacokinetics of ivabradine and the major metabolite S 18982 were evaluated in 70 pediatric patients with dilated cardiomyopathy and symptomatic chronic heart failure aged from 6 months to less than 18 years of age given ivabradine twice daily [see *Clinical Studies* (14.2)]. Ivabradine and S 18982 metabolite exposures were measured following weight-based dosing and dose titration designed to reach a dose that enables a 20% heart rate reduction without inducing bradycardia and/or signs or symptoms related to bradycardia. Analyses showed the relationship between exposure and heart rate reduction was similar across pediatric age groups and adults. Steady state exposures of ivabradine and S 18982 following maintenance doses in pediatric patients are similar to exposures achieved in adult heart failure patients given 5 mg BID.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when mice and rats received ivabradine up to 104 weeks by dietary administration. High doses in these studies were associated with mean ivabradine exposures of at least 37 times higher than the human exposure (AUC_{0-24hr}) at the MRHD.

Ivabradine tested negative in the following assays: bacterial reverse mutation (Ames) assay, *in vivo* bone marrow micronucleus assay in both mouse and rat, *in vivo* chromosomal aberration assay in rats, and *in vivo* unscheduled DNA synthesis assay in rats. Results of the *in vitro* chromosomal aberration assay

were equivocal at concentrations approximately 1,500 times the human C_{max} at the MRHD. Ivabradine tested positive in the mouse lymphoma assays and *in vitro* unscheduled DNA synthesis assay in rat hepatocytes at concentrations greater than 1,500 times the human C_{max} at the MRHD.

Reproduction toxicity studies in animals demonstrated that ivabradine did not affect fertility in male or female rats at exposures 46 to 133 times the human exposure (AUC_{0-24hr}) at the MRHD.

13.2 Animal Toxicology and/or Pharmacology

Reversible changes in retinal function were observed in dogs administered oral ivabradine at total doses of 2, 7, or 24 mg/kg/day (approximately 0.6 to 50 times the human exposure at the MRHD based on AUC_{0-24hr}) for 52 weeks. Retinal function assessed by electroretinography demonstrated reductions in cone system responses, which reversed within a week post-dosing, and were not associated with damage to ocular structures as evaluated by light microscopy. These data are consistent with the pharmacological effect of ivabradine related to its interaction with hyperpolarization-activated I_h currents in the retina, which share homology with the cardiac pacemaker I_f current.

14. CLINICAL STUDIES

14.1 Heart Failure in Adult Patients

SHIFT

The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) was a randomized, double-blind trial comparing Corlanor and placebo in 6,558 adult patients with stable New York Heart Association (NYHA) class II to IV heart failure, left ventricular ejection fraction $\leq 35\%$, and resting heart rate ≥ 70 bpm. Patients had to have been clinically stable for at least 4 weeks on an optimized and stable clinical regimen, which included maximally tolerated doses of beta-blockers and, in most cases, ACE inhibitors or ARBs, spironolactone, and diuretics, with fluid retention and symptoms of congestion minimized. Patients had to have been hospitalized for heart failure within 12 months prior to study entry.

The underlying cause of CHF was coronary artery disease in 68% of patients. At baseline, approximately 49% of randomized patients were NYHA class II, 50% were NYHA class III, and 2% were NYHA class IV. The mean left ventricular ejection fraction was 29%. All patients were initiated on Corlanor 5 mg (or matching placebo) twice daily and the dose was increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily to maintain the resting heart rate between 50 and 60 bpm, as tolerated. The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death.

Most patients (89%) were taking beta-blockers, with 26% on guideline-defined target daily doses. The main reasons for not receiving the target beta-blocker doses at baseline were hypotension (45% of patients not at target), fatigue (32%), dyspnea (14%), dizziness (12%), history of cardiac decompensation (9%), and bradycardia (6%). For the 11% of patients not receiving any beta-blocker at baseline, the main reasons were chronic obstructive pulmonary disease, hypotension, and asthma. Most patients were also taking ACE inhibitors and/or angiotensin II antagonists (91%), diuretics (83%), and anti-aldosterone agents (60%). Few patients had an implantable cardioverter-defibrillator (ICD) (3.2%) or a cardiac resynchronization therapy (CRT) device (1.1%). Median follow-up was 22.9 months. At 1 month, 63%, 26%, and 8% of Corlanor-treated patients were taking 7.5, 5, and 2.5 mg BID, whereas 3% had withdrawn from the drug, primarily for bradycardia.

SHIFT demonstrated that Corlanor reduced the risk of the combined endpoint of hospitalization for worsening heart failure or cardiovascular death based on a time-to-event analysis (hazard ratio: 0.82, 95% confidence interval [CI]: 0.75, 0.90, $p < 0.0001$) (Table 3). The treatment effect reflected only a reduction in the risk of hospitalization for worsening heart failure; there was no favorable effect on the mortality component of the primary endpoint. In the overall treatment population, Corlanor had no statistically significant benefit on cardiovascular death.

Table 3. SHIFT – Incidence of the Primary Composite Endpoint and Components

Endpoint	Corlanor (N = 3,241)			Placebo (N = 3,264)			Hazard Ratio [95% CI] p-value		
	n	%	% PY	n	%	% PY			
Primary composite endpoint: Time to first hospitalization for worsening heart failure or cardiovascular death ^a	793	24.5	14.5	937	28.7	17.7	0.82	[0.75, 0.90]	< 0.0001
Hospitalization for worsening heart failure	505	15.6	9.2	660	20.2	12.5			
Cardiovascular death as first event	288	8.9	4.8	277	8.5	4.7			
Patients with events at any time									
Hospitalization for worsening heart failure ^b	514	15.9	9.4	672	20.6	12.7	0.74	[0.66, 0.83]	
Cardiovascular death ^b	449	13.9	7.5	491	15.0	8.3	0.91	[0.80, 1.03]	

^a Patients who died on the same calendar day as their first hospitalization for worsening heart failure are counted under cardiovascular death.

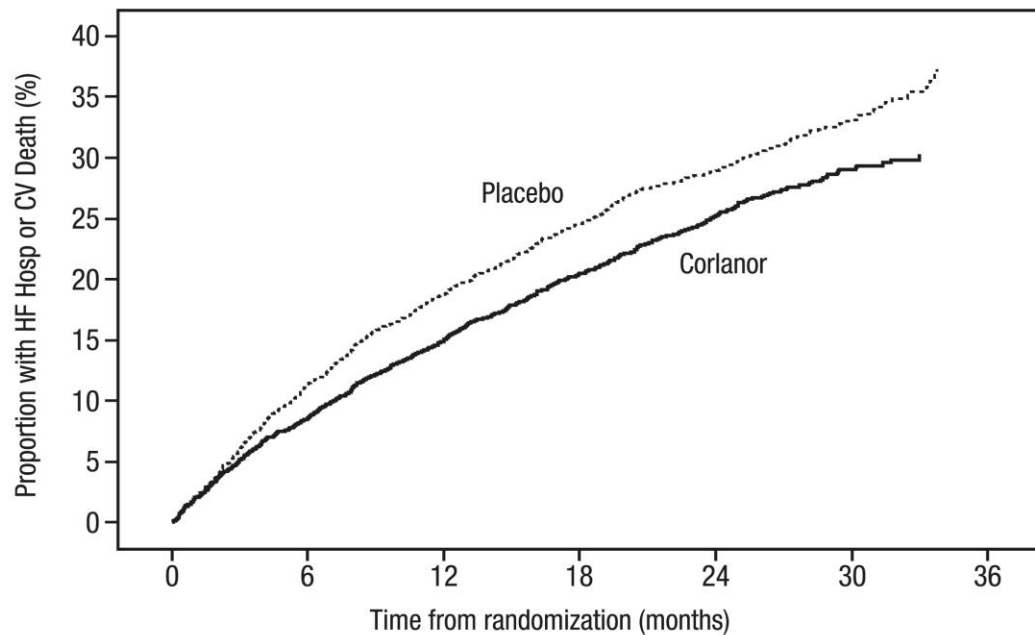
^b Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity.

N: number of patients at risk; n: number of patients having experienced the endpoint; %: incidence rate = $(n/N) \times 100$; % PY: annual incidence rate = $(n/\text{number of patient-years}) \times 100$; CI: confidence interval

The hazard ratio between treatment groups (ivabradine/placebo) was estimated based on an adjusted Cox proportional hazards model with beta-blocker intake at randomization (yes/no) as a covariate; p-value: Wald test

The Kaplan-Meier curve (Figure 3) shows time to first occurrence of the primary composite endpoint of hospitalization for worsening heart failure or cardiovascular death in the overall study.

Figure 3. SHIFT: Time to First Event of Primary Composite Endpoint



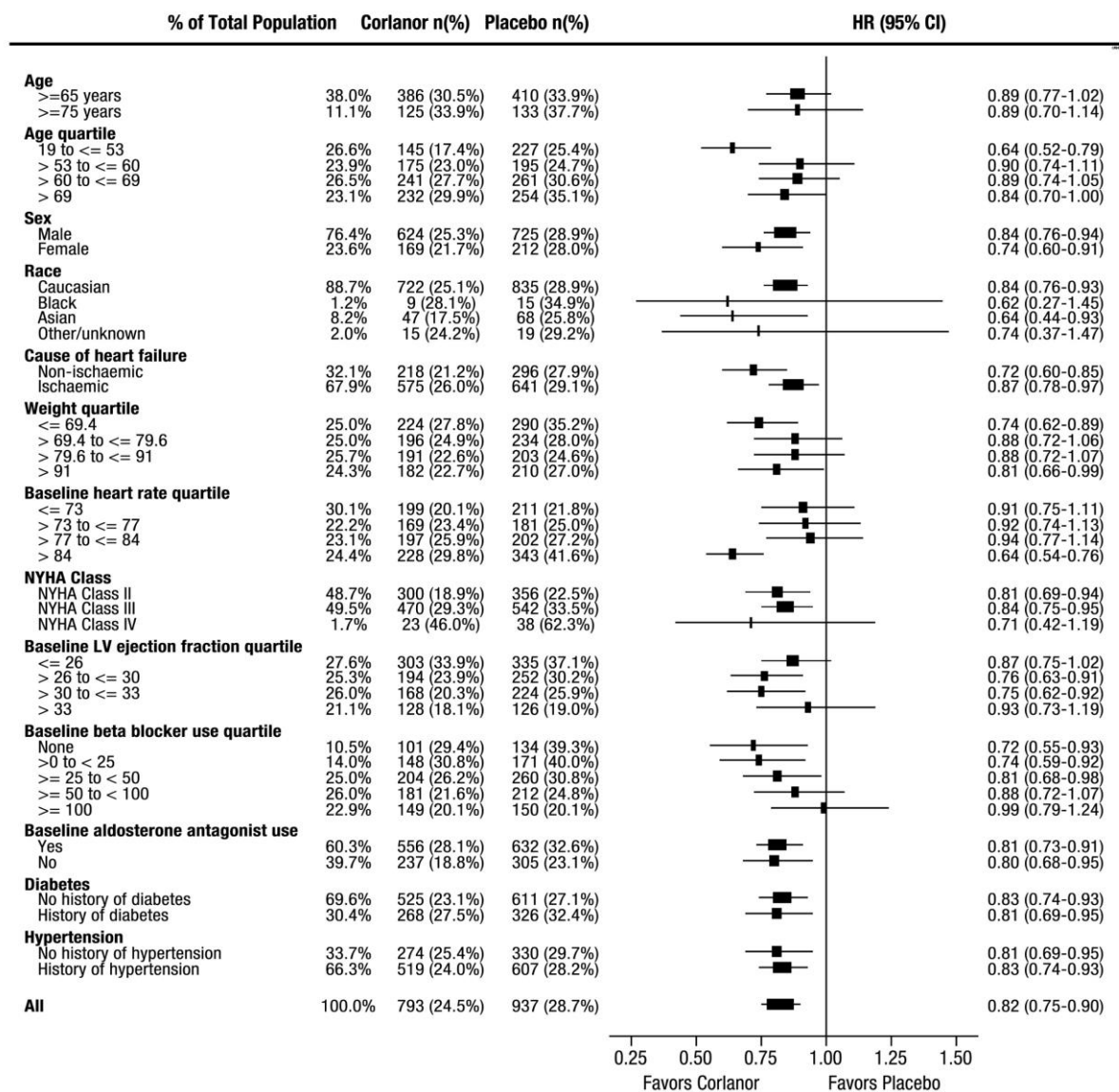
Number of Subjects at Risk:

Placebo	3264	2868	2489	2061	1089	439	17
Corlanor	3241	2928	2600	2173	1191	447	16

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. Many of these results are shown in Figure 4. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses.

Most of the results show effects consistent with the overall study result. Corlanor's benefit on the primary endpoint in SHIFT appeared to decrease as the dose of beta-blockers increased, with little if any benefit demonstrated in patients taking guideline-defined target doses of beta-blockers.

Figure 4. Effect of Treatment on Primary Composite Endpoint in Subgroups



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

BEAUTIFUL and SIGNIFY: No benefit in stable coronary artery disease with or without stable heart failure

The Morbidity-mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction Trial (BEAUTIFUL) was a randomized, double-blind, placebo-controlled trial in 10,917 adult patients with coronary artery disease, impaired left ventricular systolic function (ejection fraction < 40%) and resting heart rate ≥ 60 bpm. Patients had stable symptoms of heart failure

and/or angina for at least 3 months and were receiving conventional cardiovascular medications at stable doses for at least 1 month. Beta-blocker therapy was not required, nor was there a protocol mandate to achieve any specific dosing targets for patients who were taking beta-blockers. Patients were randomized 1:1 to Corlanor or placebo at an initial dose of 5 mg twice daily with the dose increased to 7.5 mg twice daily depending on resting heart rate and tolerability. The primary endpoint was the composite of time to first cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new-onset or worsening heart failure. Most patients were NYHA class II (61.4%) or class III (23.2%) - none were class IV. Through a median follow-up of 19 months, Corlanor did not significantly affect the primary composite endpoint (HR 1.00, 95% CI = 0.91, 1.10).

The Study Assessing the Morbi-mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease Trial (SIGNIFY) was a randomized, double-blind trial administering Corlanor or placebo to 19,102 adult patients with stable coronary artery disease but without clinically evident heart failure (NYHA class I). Beta-blocker therapy was not required. Corlanor was initiated at a dose of 7.5 mg twice daily and the dose could be increased to as high as 10 mg twice daily or down-titrated to 5.0 mg twice daily to achieve a target heart rate of 55 to 60 bpm. The primary endpoint was a composite of the first occurrence of either cardiovascular death or myocardial infarction. Through a median follow-up of 24.1 months, Corlanor did not significantly affect the primary composite endpoint (HR 1.08, 95% CI = 0.96, 1.20).

14.2 Heart Failure in Pediatric Patients

Because Corlanor was effective in improving outcomes in patients with dilated cardiomyopathy (DCM) in SHIFT, the effect on heart rate was considered a reasonable basis to infer clinical benefits in pediatric patients with DCM. Thus, Corlanor was evaluated for its effect on heart rate in a multi-center, randomized, double-blind, placebo-controlled trial in children with symptomatic DCM. The study collected data from 116 patients aged 6 months to less than 18 years with DCM in sinus rhythm, NYHA/Ross class II to IV heart failure, and left ventricular ejection fraction \leq 45%. Patients had to be clinically stable for at least 4 weeks and on optimized medical therapy with a resting heart rate (HR) complying with the following criteria:

- HR \geq 105 bpm in the age-subset 6–12 months.
- HR \geq 95 bpm in the age-subset 1–3 years.
- HR \geq 75 bpm in the age-subset 3–5 years.
- HR \geq 70 bpm in the age-subset 5–18 years.

Patients were randomized in a 2:1 ratio to receive Corlanor or placebo. Doses of study medication were titrated over a 2- to 8-week period to achieve a 20% heart rate reduction without inducing bradycardia.

The target heart rate reduction was obtained at the end of the titration period in a significantly higher proportion of patients with Corlanor vs. placebo (72% vs. 16% respectively; Odds Ratio = 15; 95% CI = [5; 47]). A statistically significant reduction in HR was observed with Corlanor compared to placebo at the end of the titration period (-23 ± 11 bpm vs. -2 ± 12 bpm respectively).

16. HOW SUPPLIED/STORAGE AND HANDLING

Tablets:

Corlanor (ivabradine) 5 mg tablets are formulated as salmon-colored, oval-shaped, film-coated tablets functionally scored on both edges, marked with “5” on one face and bisected on the other face. They are supplied as follows:

- Bottles of 60 tablets with child-resistant closure (NDC 55513-800-60)

Corlanor (ivabradine) 7.5 mg tablets are formulated as salmon-colored, triangular-shaped, film-coated tablets debossed with “7.5” on one face and plain on the other face. They are supplied as follows:

- Bottles of 60 tablets with child-resistant closure (NDC 55513-810-60)

Oral Solution:

Corlanor (ivabradine) oral solution is a colorless liquid supplied in an opaque, low density polyethylene (LDPE) plastic ampule. Each 5 mL ampule is individually packaged in a child-resistant foil pouch and supplied in cartons containing 28 foil pouches. Corlanor oral solution is supplied as 5 mg/5 mL (1 mg/mL) (NDC 55513-813-01).

Storage

Store Corlanor tablets and oral solution at 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see *USP Controlled Room Temperature*]. Protect Corlanor ampule from light by storing in the foil pouch until use.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling [see *Medication Guide and Instructions for Use*].

- Fetal Toxicity

Advise pregnant women of the potential risks to a fetus.

Advise females of reproductive potential to use effective contraception and to notify their healthcare provider with a known or suspected pregnancy [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.1), (8.3)*].

- Low Heart Rate

Advise patients to report significant decreases in heart rate or symptoms such as dizziness, fatigue, or hypotension [*see Warnings and Precautions (5.3)*].

- Atrial Fibrillation

Advise patients to report symptoms of atrial fibrillation, such as heart palpitations or racing, chest pressure, or worsened shortness of breath [*see Warnings and Precautions (5.2)*].

- Phosphenes

Advise patients about the possible occurrence of luminous phenomena (phosphenes). Advise patients to use caution if they are driving or using machines in situations where sudden changes in light intensity may occur, especially when driving at night. Advise patients that phosphenes may subside spontaneously during continued treatment with Corlanor [*see Adverse Reactions (6.1)*].

- Drug Interactions

Advise patients to avoid ingestion of grapefruit juice and St. John's wort [*see Drug Interactions (7.1)*].

- Intake with Food

Advise patients to take Corlanor twice daily with food [*see Dosage and Administration (2)*].

- Oral Solution

Advise parents/caregivers on preparation and administration instructions including the use of a calibrated oral syringe and a medicine cup (provided by the pharmacy) to avoid dosing errors [*see Dosage and Administration (2.2)*].

Advise parents/caregivers that the oral solution should not be administered by the child.

Advise parents/caregivers to not double up doses (e.g., if patient spits out the drug or caregiver forgets to give the drug at the prescribed time).

Advise parents/caregivers to throw away the unused product remaining in the cup immediately after drawing up the prescribed dose in the syringe.



Corlanor® (ivabradine)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: <http://pat.amgen.com/Corlanor/>

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