PDL NEW DRUG REVIEW

Proprietary Name: Corlanor®
Common Name: ivabradine
PDL Category: Sinus Node Inhibitors

Summary

Indications and Usage: To reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35%, who are in sinus rhythm with resting heart rate ≥70 beats per minute (bpm) and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

The use of Corlanor® is not recommended in those with demand pacemakers set to rates ≥60 bpm.

There is no pregnancy category listed for this product; however, the risk summary suggests that based on animal findings, Corlanor® may cause fetal harm if given to pregnant women. There are no adequate and well-controlled studies of use in pregnant women. Pregnant women should be advised of the potential risk to the fetus. In addition, it is recommended to advise use of effective contraception during treatment. The safety and efficacy of use in children under the age of 18 years have not been established.

Dosage Forms: Film-coated Tablets: 5mg (scored), 7.5mg

Recommended Dosage: Take 5mg BID with meals; in those with a history of conduction defects or other patients in whom bradycardia could lead to hemodynamic compromise, start at 2.5mg BID before increasing the dose based on heart rate. After 2 weeks, assess and adjust dose to achieve resting heart rate between 50-60bpm per the table below. Thereafter, adjust dose per resting heart rate and tolerability as needed to a max dose of 7.5mg BID.

Heart Rate	Dose Adjustment
>60bpm	↑ dose by 2.5mg (given BID) to max of 7.5mg BID
50-60bpm	Maintain dose
<50bpm or signs/symptoms of bradycardia	↓ dose by 2.5mg (given BID); if current dose is 2.5mg BID, then discontinue therapy

Dose adjustments are not required in those with creatinine clearance (CrCl) 15-60ml/min; however, there is no data available for use in those with CrCL <15ml/min. Dose adjustments are not required in those with mild or moderate hepatic impairment; however, use is contraindicated in those with severe hepatic impairment.

Drug Interactions: Corlanor® is primarily metabolized by CYP3A4. The concomitant use of strong CYP3A4 inhibitors (e.g. azole antifungals such as itraconazole, macrolide antibiotics such as clarithromycin or telithromycin, HIV protease inhibitors such as nelfinavir, and nefazodone) with Corlanor® is contraindicated. It is recommended

to avoid concomitant use of moderate CYP3A4 inhibitors (such as diltiazem, verapamil, and grapefruit juice) with Corlanor®. Last, it is recommended to avoid concomitant use of CYP3A4 inducers (such as St. John's wort, rifampicin, barbiturates, and phenytoin) with Corlanor®.

It is recommended to monitor heart rate if taking Corlanor® with drugs that slow the heart rate (e.g. digoxin, amiodarone, beta-blockers).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Corlanor®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than placebo.* The most frequently reported adverse events included bradycardia (7.8%), hypertension, blood pressure increased (1.1%), atrial fibrillation (1.7%), and phosphenes (visual brightness (2.3%)). The onset of phosphenes caused by Corlanor® is typically within the first 2 months of treatment, and they may repeatedly occur. Nevertheless, the phosphenes were mostly mild to moderate intensity and led to <1% treatment discontinuation.

There is an increased risk of atrial fibrillation (a-fib) with Corlanor®. In clinical studies, the rate of a-fib was 5% per patient-year in the Corlanor®-treated group vs 3.9% per patient-year with the placebo-treated group. It is recommended to regularly monitor cardiac rhythm and to discontinue Corlanor® treatment if a-fib develops.

Bradycardia, sinus arrest, and heart block have also occurred in those treated with Corlanor®. It is recommended to avoid use of Corlanor® in those with 2nd degree atrioventricular block, unless a functional demand pacemaker is present.

Contraindications: Acute decompensated heart failure; Blood pressure <90/50mmHg; Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present; Resting heart rate <60bpm prior to treatment; Severe hepatic impairment; Pacemaker dependence (heart rate maintained exclusively by the pacemaker); and Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors.

Manufacturer: Amgen

Analysis: Ivabradine, the active ingredient of Corlanor®, 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. There were no effects on ventricular repolarization and no effects on myocardial contractility. In clinical trials, the cardiac effects were most pronounced in the sinoatrial (SA) node.

A randomized, double-blind study (the Systolic Heart failure treatment with I_f inhibitor ivabradine Trial [SHIFT trial] was performed to assess the safety and efficacy of Corlanor® in adults (N=6558) with stable New York Heart Association (NYHA) class II to IV heart failure, left ventricular ejection fraction ≤35%, and resting heart rate ≥70bpm. Participants had to have been hospitalized for heart failure within 12 months prior to study entry. Most (89%) were taking beta-blockers. The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death.

Results of this study suggested that Corlanor® reduced the risk of the combined endpoint of hospitalization for worsening heart failure or cardiovascular death (24.5% vs 28.7%; hazard ratio [HR] 0.82; p<0.0001; NNT 24). The effect reflected only a reduction in the risk of hospitalization for worsening heart failure (15.6% vs 20.2%), as there was no favorable effect on the CV mortality component of the primary endpoint (8.9% vs 8.5%).

The BEAUTIFUL (N=10,917) and the SIGNIFY (N=19,102) studies were both randomized, double-blind, placebo-controlled studies that included adults with coronary artery disease. The primary endpoint in the BEAUTIFUL study was the composite of time to first cardiovascular death, hospitalization for acute MI, or hospitalization for new-onset or worsening heart failure. With a median 19 months follow-up, results suggested that Corlanor® did not significantly affect the primary composite endpoint (HR 1). The primary endpoint in the SIGNIFY study was a

composite of the first occurrence of either cardiovascular death or myocardial infarction. With a median 24 months, results suggested that Corlanor® did not significantly affect the primary composite endpoint (HR 1.08).

Place in Therapy: One noted reference source suggests "although both beta-blockers and ivabradine reduce heart rate, the evidence for beta blockade is much stronger, and the available evidence does not support use of ivabradine as a full or partial substitute for beta blocker therapy for HF."[2] Corlanor® is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35%, who are in sinus rhythm with resting heart rate ≥70 beats per minute (bpm) and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

There is no consistent evidence at this time to support that Corlanor® is safer or more effective than the currently available, more cost effective medications, based on data reviewed from registration trials in the package insert as well as a review of current treatment recommendations for heart failure. It is therefore recommended that Corlanor® remain non-preferred and require prior authorization and be available to the few who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Corlanor [package insert]. Thousand Oaks, CA: Amgen Inc; 2015.

[2] UpToDate desktop version. Investigational and emerging therapies for heart failure. Accessed May 2015.