

## **FDA approves Corlanor (ivabradine) to treat heart failure**

Heart failure, sometimes known as congestive heart failure, occurs when the heart muscle doesn't pump blood as well as it should. Certain conditions, such as narrowed arteries in the heart (coronary artery disease) or high blood pressure, gradually leave the heart too weak or stiff to fill and pump efficiently. Heart failure is a leading cause of death and disability in adults.

Not all conditions that lead to heart failure can be reversed, but treatments can improve the signs and symptoms of heart failure and help to live longer. Lifestyle changes — such as exercising, reducing salt in the diet, managing stress and losing weight — can improve quality of life.

One way to prevent heart failure is to control conditions that cause heart failure, such as coronary artery disease, high blood pressure, diabetes or obesity.

**On April,15, 2015**, The U.S. Food and Drug administration approved corlanor (ivabradine) for use in certain people who have long-lasting (chronic) heart failure caused by the lower-left part of their heart not contracting well, to reduce hospitalization from worsening heart failure.

Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker *If* current that controls the spontaneous diastolic depolarization in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarization. It is indicated for patients who have symptoms of heart failure that are stable, a normal heartbeat with a resting heart rate of at least 70 beats per minute and are also taking beta blockers at the highest dose they can tolerate.(\*)

The Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) demonstrated that heart rate reduction with the If inhibitor, ivabradine, significantly improved clinical outcomes in patients with chronic systolic HF. In this study. Michele Robertson and his colleges, Comprised 712 patients with severe (defined previously) and 5,973 with less severe (NYHA "New York Heart Association" classes II or III and LVEF >20%) HF, all randomized to ivabradine or placebo on a background of guideline-defined standard care.

In this post hoc analysis, the effect of ivabradine on outcomes according to the severity of HF at baseline was assessed. Patients with severe HF were defined as all patients in NYHA class IV and NYHA classes II or III with LVEF ≤20%. The complementary group of patients with less severe HF were those in classes II or III with LVEF >20%. To test the relevance of the results in patients with severe HF according to this definition, the following subgroups were also analyzed: patients in NYHA class IV; patients in NYHA classes II or III with LVEF ≤20%; patients in NYHA classes II or III with LVEF ≤15%; and patients in NYHA class IV with LVEF ≤15%, and the effect in patients with severe or less severe HF and heart rate at rest ≥75 beats/min at baseline.

The primary outcome was the composite of cardiovascular death or hospitalization for worsening HF. Other end points included the individual components of the primary end point, all-cause death, HF death, and hospitalization for any cause.

In the group with severe HF and heart rate  $\geq 75$  beats/min, ivabradine was associated with significant reductions versus placebo in risk for the primary composite end point, all-cause death, cardiovascular death, HF death, and hospitalization for worsening HF. Ivabradine had an acceptable safety profile, largely indistinguishable from that of placebo. The inclusion of ivabradine in the regimen of patients with severe HF is safe and can improve outcomes, even when  $\beta$  blockers are also administered. (1)

In a double-blind, placebo-controlled, crossover study Twenty-one patients with inappropriate sinus tachycardia were randomized to receive placebo (n = 10) or ivabradine 5 mg twice daily (n = 11) for 6 weeks. After a washout period, patients crossed over for an additional 6 weeks. Each patient underwent symptom evaluation and heart rate assessment at the start and finish of each phase. After taking ivabradine, patients reported elimination of  $>70\%$  of symptoms, with 47% of them experiencing complete elimination.

These effects were associated with a significant reduction of heart rate at rest (from  $88 \pm 11$  beats/min to  $76 \pm 11$  beats/min,) on standing (from  $108 \pm 12$  beats/min to  $92 \pm 11$  beats/min) during 24h (from  $88 \pm 5$  beats/min to  $77 \pm 9$  beats/min) and during effort (from  $176 \pm 17$  beats/min to  $158 \pm 16$  beats/min).

Ivabradine administration was also associated with a significant increase in exercise performance. No cardiovascular side effects were observed in any patients while taking ivabradine.

In this study, ivabradine significantly improved symptoms associated with inappropriate sinus tachycardia and completely eliminated them in approximately half of the patients. These findings suggest that ivabradine may be an important agent for improving symptoms in patients with inappropriate sinus tachycardia. (2)

In a randomized double-blind, parallel-group study, The aim of the study is that patients with Low systolic blood pressure (SBP) is associated with poor outcomes in heart failure and complicates management. In a post hoc analysis, Michel Komajda and his colleagues investigated the efficacy and safety of ivabradine in the SHIFT population divided by tertiles of baseline SBP. Michel Komajda and his colleagues comprised 2110 patients with SBP  $<115$  mmHg, 1968 with  $115 \leq$  SBP  $<130$  mmHg, and 2427 with SBP  $\geq 130$  mmHg. Patients with low SBP were younger, had lower ejection fraction, and were less likely to be at target beta-blocker dose than patients in the other SBP groups. Ivabradine was associated with a similar relative risk reduction of the composite outcome in the three SBP groups SBP  $<115$  mmHg. Similar results were found for cardiovascular, hospitalization because of heart failure, all-cause mortality, and heart failure mortality. There was no evidence for a difference in safety profile according to SBP group. Results was the efficacy and safety of ivabradine is independent of SBP. This may have implications for the management of HF patients with low SBP and elevated heart rate. (3)

In conclusion, our analysis confirms that heart rate reduction with ivabradine can be safely used in severe HF and may improve clinical outcomes independently of disease severity.

## References

(\*) [www.fda.gov](http://www.fda.gov) last accessed 18/7/2015

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm442978.htm>

(1) Michele Robertson, Luigi Tavazzi , Karl Swedberg, et al. Efficacy and Safety of Ivabradine in Patients With Severe Chronic Systolic Heart Failure. The American Journal of Cardiology.2014;13:497-503.

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(3) Michel Komajda, Michael Böhm, Jeffrey S Borer, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. European Journal of Heart Failure.2014;16:810-816

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