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Press Release

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PROCORALAN MAKING A STRONG ENTRY TO THE NEW ESC GUIDELINES FOR THE MANAGEMENT OF HEART FAILURE

The new ESC guidelines for the diagnosis and management of heart failure include the heart rate–lowering drug, **Procoralan®** (ivabradine)

June 6, 2012, Paris: Less than 2 years after the publication in The Lancet of the SHIFT study results demonstrating its benefits in heart failure, Procoralan® is now integrated in the new ESC guidelines for the management of heart failure.[1]

The guidelines, just presented at the ESC's Heart Failure Congress in Belgrade, Serbia, have been updated for the first time since 2008. They make recommendations for treatment based upon evidence for established and new diagnostic tests, and therapies for heart failure.

"The revised ESC Heart Failure guidelines aim to help physicians in everyday clinical medical decision-making and if implemented offer a real opportunity to improve the outcome of patients with this condition," commented John McMurray, Professor of Medical Cardiology at the University of Glasgow and principal author of the new ESC guidelines. Heart failure patients with elevated heart rates are at a significantly greater risk of death or hospitalisation, which both impacts patients' quality of life and ultimate outcome and puts pressure on healthcare systems.[2]

In addition, a new indication for ivabradine in chronic heart failure was granted by the European Medicines Agency in February 2012. This was based on new data from the SHIFT study[3] in which patients with an elevated heart rate of greater than or equal to 75 beats per minute (bpm) showed a significant reduction in the primary composite endpoint (CV death and hospitalisation for worsening heart failure) of 24% ($p<0.0001$), reduction in risk of cardiovascular death by 17% ($p=0.0166$), all-cause death by 17% ($p=0.0109$) and heart failure hospitalisation by 30% ($p<0.0001$).

The new indication and the new ESC guidelines for the management of heart failure are the two major advances which will allow heart failure patients to benefit from ivabradine.

About chronic heart failure

Chronic heart failure affects 15 million patients in Europe (2% to 3% of the overall population).[4] It is a disabling condition and, despite improvements in treatment and management, generally has a poor prognosis. Heart failure impairs the heart's ability to pump effectively and to maintain sufficient circulation to meet the body's needs. It is most commonly caused by acute (myocardial infarction) or chronic (angina pectoris) ischaemia (coronary artery disease).[5, 6]

About ivabradine

Procoralan® (ivabradine) is the only drug to reduce heart rate selectively by inhibiting one of the electrical signals that determine heart rate—the pacemaker I_f current.[3] Procoralan reduces heart rate without significantly impacting the ability of the heart muscle to pump blood.[3,9]

Procoralan was launched in January 2006 for the treatment of stable angina. It is indicated in the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal (sinus) rhythm unable to tolerate or with a contraindication to the use of beta-blockers or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is >60 bpm.[3]

Procoralan was subsequently approved by the European Commission for the treatment of patients with chronic heart failure in February 2012. It is indicated in the treatment of chronic heart failure in patients with normal (sinus) rhythm and whose heart rate is 75 bpm or above, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.[8] The decision to authorise the indication for Procoralan in heart failure followed the review of data from the SHI_fT trial, the largest ever morbidity-mortality study of treatments for chronic heart failure involving more than 6000 patients. It demonstrated that the treatment significantly reduced the risk of death and hospitalisation for heart failure, and improved the quality of life of people living with the disease.[10,11] This reduction in mortality was highly significant in patients with a heart rate of 75 bpm or above, for whom Procoralan is now indicated.[3]

Depending on the country, ivabradine is available as Procoralan(R), Coralan(R), Coraxan(R), or Corlentor(R)

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NOTES TO EDITORS

About the SHI_fT study

SHI_fT (**S**ystolic **H**eart failure treatment with the I_f inhibitor ivabradine **T**rial) is a randomised, double-blind, placebo-controlled study involving 6505 people in 37 countries. This study set out to evaluate whether the addition of the I_f inhibitor, Procoralan, to optimal guidelines-based treatment improves cardiovascular outcomes in patients with moderate to severe chronic heart failure, reduced left ventricular ejection fraction and heart rate of 70 bpm or above.[10]

SHI_fT showed that the I_f inhibitor Procoralan reduced the risk of the primary composite endpoint (CV death and hospitalisation for worsening heart failure) by 18% (p<0.0001), death from heart failure by 26% (p=0.014), and the risk of hospitalisation by 26% (p<0.0001). The benefits were seen even though the study patients were already taking currently recommended heart failure treatments.[9] In the subgroup of patients with heart rate above 75 bpm at baseline (n = 4150), Procoralan reduced the risk of the primary composite endpoint (CV death and hospitalisation for worsening heart failure) by 24 % (p<0.0001), cardiovascular death by 17% (p=0.0166), and all-cause death by 17% (p=0.0109).

A pre-specified sub-study of 1944 patients from the main study population showed that the reduction in heart rate achieved through treatment with Procoralan was associated with almost double the improvement in quality of life compared with the control group. This improvement was observed in both the disease-related component and the social component of the scores.[11]

Quality of life assessments were conducted using the Kansas City Cardiomyopathy Questionnaire, a 23-item, self-administered questionnaire which quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life.[11]

In an echocardiography sub-study, Procoralan was shown to lead to a reduction in the heart's left ventricular end-systolic volume (the blood volume remaining in the left ventricle after contraction), which resulted in improved efficiency of the left ventricle and of overall heart function.[12]

About the BEAUTIFUL study

BEAUTIFUL (mor**B**idity-mortality **E**v**A**l**U**a**T**ion of the I_f inhibitor ivabradine in patients with coronary heart disease and left ventric**UL**ar dysfunction) was a randomised, double-blind, placebo-controlled study involving 10 917 people in 33 countries. The study set out to evaluate whether mortality and morbidity would be reduced by the addition of the selective heart rate–lowering treatment, ivabradine, to current therapy in patients with stable CAD and LV systolic dysfunction.[13] On entering the trial 87% of patients were receiving beta-blockers, 89% renin-angiotensin system agents, 94% antithrombotic agents, 76% lipid-lowering agents, and 12% calcium channel blockers. 37% of patients also had diabetes and 40% had metabolic syndrome.[14]

The main efficacy criterion was the composite of cardiovascular death, hospitalisation for acute MI or hospitalisation for new-onset or worsening heart failure. While the study showed no difference in the rate of the primary composite outcome in the ivabradine group by comparison with the placebo group, an over one third (36%) reduction in risk of hospitalisation for fatal or non-fatal heart attack was shown in a broad range of patients with stable coronary artery disease (CAD) and left ventricular dysfunction with heart rate ≥70 bpm. The drug also reduced by 30% (ARR = 1%) the risk of patients having to undergo revascularisation procedures.[13] In a subgroup of patients with limiting angina (n=1507), the benefit of ivabradine was even more pronounced, with a 24% reduction in the primary endpoint and a 42% reduction in the risk of hospitalisation for fatal or non-fatal heart attack (ARR = 2.7%, p=0.021)).[15] In those with an elevated heart rate (>70 bpm) the risk was reduced by 73% (ARR = 4.6%, p=0.002).[15]

About Servier

Servier is France's leading independent pharmaceutical company and the country's second largest drug company. Servier is present in 140 countries. R&D at Servier spans a range of therapeutic fields, with the main areas of focus being cardiovascular disease, neuroscience, cancer, metabolic disorders, and rheumatology. In the field of cardiovascular disease in particular, Servier is one of the principal research organisations dedicated to the development of new medicines. Servier has a long-standing interest in the field of cardiovascular disease, as attested by the fact that 63% of Servier's global turnover from medicines is made up of drugs targeting cardiovascular diseases.

References

1. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J*. DOI:10.1093/eurheart/ehs104
2. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Fail*. 2002;4:361-371
3. Böhm M, Borer J, Ford I et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol.* DOI 10.1007/s00392-012-0467-8
4. European Society of Cardiology (ESC). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J.* 2008; 29: 2388-2442.NICE guidelines for the management of chronic heart failure in adults in primary and secondary care. Available at www.nice.org.uk/nicemedia/live/13099/50517/50517.pdf (Last accessed May 22, 2012)
5. Juenger J, Schellberg D, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart.* 2002; 87:235-241.
6. Fox K *et al.* Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet*. 2008; 372: 817-821
7. Procoralan Summary of Product Characteristics. www.emc.medicines.org.uk (Last accessed May 22, 2012)
8. Andrews TC, et al. Subsets of ambulatory myocardial ischemia based on heart rate activity. Circadian distribution and response to anti-ischemic medication. The Angina and Silent Ischemia Study Group (ASIS). *Circulation* 1993; 88: 92-100
9. DiFrancesco D and Camm JA. Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs*. 2004; 64(16): 1757–1765.
10. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010; 376:875-85
11. Ekman I, Chassany O, Komajda M et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. *Eur Heart J.* 2011; 32:2395-2404.
12. Tardif JC, O'Meara E, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. *Eur Heart J.* 2011, DOI: 10.1093/eurheartj/ehr311. Available at http://eurheartj.oxfordjournals.org/
13. Fox K, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008; 372, :807–816.
14. Fox K, et al. Rationale and design of a randomized, double-blind, placebo-controlled trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction: the morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) Study. *Am Heart J*. 2006; 152: 860-866
15. Fox K et al. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized controlled BEAUTIFUL trial. *Eur Heart J.* 2009; 30: 2337-2345