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Forthcoming cardiology meetings:

American College of Cardiology (ACC)
29th March to 1st April 2008 Chicago, Illinois, USA
Web site: www.acc.org

16th World Congress of Cardiology (WCC)
18th to 21st May 2008 Buenos Aires, Argentina
Web site: www.worldcardiocongress.org

EUROPREVENT 2008
1st to 3rd May 2008 Paris, France
Web site: www.esccardio.org/Europrevent/europrevent2008

The 28th Annual Meeting of the International Society for Heart Research (ISHR)
– European section
28th to 31st May 2008 Athens, Greece
Web site: www.usouthal.edu/ishr

Heart Failure 2008
14th to 17th June 2008 Milan, Italy

European Society of Cardiology (ESC) Congress 2008
30th August to 3rd September 2008 Munich, Germany
Web site: www.escardio.org

5th Global Cardiovascular Clinical Trialists Forum (CVCT)
25th to 27th September 2008 Cannes, France
Web site: www.globalcvctforum.com
Epidemiological studies have shown that heart rate (HR) is a significant risk factor for cardiovascular morbidity and mortality. Our recent literature review of all 38 epidemiological studies of HR examined the association between HR and morbidity-mortality. Following adjustment for other risk factors, only two studies for all-cause mortality and four studies for cardiovascular mortality reported an absence of association between HR and mortality. All other studies show elevated heart rate to be strongly associated with increased risk of all-cause morbidity and mortality, the relationship of which is independent of other factors—such as BP and physical activity—and generally stronger in males than females. Interestingly, these studies show that the increase in the cardiovascular risk, associated with elevated HR, was comparable to the increase in risk observed with high blood pressure. Moreover, an increase in HR by 20 bpm was associated with an increase in the risk of cardiac death by 40%, which is comparable with mortality figures seen with an increase in systolic blood pressure by 20 mm Hg. Recently, the Ohasama study showed that an increase in home-measured resting HR by 5 bpm was associated with a 17% increase in 10-year cardiovascular (CV) mortality. It has also been shown that HR recorded in elderly men has a strong predictive value in survival to a very old age. Thus, men with HR >80 bpm have a reduced probability, by more than 40%, of reaching 85 years of age as compared with men of the same age with a HR of less than 60 bpm (Figure 1).

Taken together, these results indicate that the risk associated with elevated HR is not only statistically significant, but also clinically relevant and thus should be considered when evaluating patients.

The mechanisms that explain the connection between elevated HR, hypertension, atherosclerosis, and cardiovascular events have also been documented in many laboratory and clinical studies. Tachycardia may reflect an altered balance of the autonomic nervous system tone. However, although high sympathetic activity alone could explain the precipitation of a cardiovascular event in a subject with elevated HR, a direct link between high HR and both the formation of the atherosclerotic lesion and the occurrence of the cardiovascular event has also been proven. Heart rate, as a component of CV pulsatile stress, may have a direct effect on the cardiovascular system since it increases myocardial oxygen consumption and induces fatigue and fracture of elastic fibers within the arterial wall. In monkeys, plaque formation in carotid atherosclerosis correlates positively with HR, whereas lowering the HR delayed aortoiliac atherosclerosis. Recent clinical studies have shown significant associations between HR and functional alterations of large arteries, mainly arterial stiffness. Hypertensive subjects with high HR showed a more pronounced progression in arterial stiffness over a period of 6 years as compared with subjects with low HR (Figure 2).

Although the association between elevated HR and cardiovascular morbidity and mortality has been demonstrated in a large number of epidemiologic studies, HR has remained a neglected cardiovascular risk factor until very recently. In June 2007, the European Society of Cardiology (ESC) and the European Society of Hypertension in the Guidelines for the Management of Hypertension, stated that “There may be reasons to include an elevated HR as a risk factor because of a growing body of evidence that elevated HR values relate to the risk of cardiovascular morbidity and mortality as well as all-cause mortality.”

![Figure 1. Probability of survival at an old age, according to heart rate at the age of 60 to 70 years after adjustment for age, systolic blood pressure, smoking and physical activity.](image-url)
Similarly, the ESC guidelines on cardiovascular disease prevention now recommend avoidance of elevated resting HR in the general population—achieved through regular physical activity, and avoidance of stress and excessive use of stimulants, such as caffeine—and pharmacological intervention to reduce heart rate in post-myocardial infarction patients and those with congestive heart failure. Consequently, for the first time, HR is considered as an independent risk factor and, therefore, is a potential target for pharmacological therapies, particularly in high-risk patients.

According to the current data, it would seem reasonable to consider a HR higher than 85 bpm as a risk factor. Since a fast HR per se causes cardiovascular damage, all drugs that lower HR have the potential of further reducing cardiovascular events in patients with elevated HR. The f-channel inhibitor Procoralan (ivabradine) is a selective HR-lowering agent with no effect on blood pressure. Recent animal studies have shown that HR decrease with Procoralan lead to a significant reduction of intima-media hypertrophy (Figure 3) and improvement in the elastic properties of the arterial wall. Large ongoing clinical trials with Procoralan will assess the value of this new compound in the prevention of cardiovascular events in high-risk CAD patients.
Heart rate and Cardiovascular risk

References

The benefits of heart rate reduction in human beings: recent developments

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The global burden of heart disease is increasing, both in the Western world and particularly in developing countries. The benefit seen from treatments seem to have reached a plateau. Data from the recent Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation (COURAGE) trial show a significant proportion of stable angina patients manifest ongoing limiting symptoms despite optimal medical therapy or angioplasty (Figure 1). Even in higher-risk patient populations, such as following ST-segment–elevation myocardial infarction (STEMI), effective therapy is hard to apply—up to 10% of patients are acutely intolerant of β-blockade, and a further 30% discontinue β-blocker therapy by 12 months (Figure 2). The highest-risk patients, those with left ventricular (LV) impairment and heart failure, are most in need of novel therapies. While angiotensin-converting enzyme (ACE) inhibition and β-blockade have brought huge clinical benefits, further neuroendocrine manipulation with omapatrilat or endothelin antagonists has not, and device therapy appears to have achieved its full clinical potential. Treatment gaps remain, with continued impaired quality of life and life expectancy for tens of millions worldwide.

Resting heart rate (HR) has long been identified as an independent predictor of mortality in both healthy and diseased hearts. Only recently have studies demonstrated the crucial importance of HR lowering in mediating the benefits of medical therapy in angina and particularly in heart failure. Ivabradine (Procoralan®) is a novel If current–inhibiting agent able to selectively and effectively lower HR in patients with angina or heart failure when in sinus rhythm. Procoralan is the first new anti-ischemic agent available to patients in over 10 years and represents a potentially important therapeutic avenue. As

![Figure 1](image1.png)

**Figure 1.** Angioplasty and stenting (PCI, percutaneous coronary intervention) vs optimal medical therapy (OMT) in stable coronary artery disease with angina. Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation (COURAGE) trial.

<table>
<thead>
<tr>
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<th>PCI+OMT</th>
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<tbody>
<tr>
<td>Baseline</td>
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<tr>
<td>5 Years</td>
<td>74%</td>
<td>72%</td>
</tr>
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</table>

![Figure 2](image2.png)

**Figure 2.** The steady attrition in the compliance with β-blocker medication post myocardial infarction, and poor uptake in those not leaving hospital on a β-blocker.
The benefits of heart rate reduction in human beings: recent developments

such, Procoralan has gained a license in Europe for use in stable angina and has rapidly been incorporated into the European Society Guidelines in this setting (Figure 3).6

Heart rate reduction without unwanted effects

Identifying the beneficial role of HR lowering among the actions of β-blockers in heart failure has proved challenging. β-Blockers cause many unwanted side effects, such as reduced skeletal muscle blood flow, bronchoconstriction, altered glucose metabolism, and sexual dysfunction—leading to poor compliance or impaired quality of life. Thackeray and co-workers studied the role of pure HR lowering in heart failure patients using permanent pacemakers and in whom HR could be controlled reliably.7 Two groups of patients were randomized to long-term pacing with a lower HR of 60 beats per minute (bpm) or a higher HR of 80 bpm. All patients received carvedilol at a dose of at least 25 mg/d. Using positive LV remodeling as a surrogate marker for improved survival, LV volumes with gated blood pool scans were used at baseline and 12 months. Beneficial positive remodeling was virtually absent in the group of patients with the higher HR, and seen in the majority of those at the lower HR (Figure 4). Of note, over one third of patients entering the study died during the study period—reinforcing the major impact heart failure has on survival, despite “optimal” therapy. The potential benefit that Procoralan may confer on these patients is of great importance. To be able to offer most, or perhaps all, of the benefits of systemic adrenergic blockade—without the well-recognized side effects—would certainly improve quality of life, uptake of therapy, compliance with therapy, and, therefore, the overall magnitude of HR lowering achieved. Intention-to-treat analysis may well show superior outcomes for the agent that patients prefer to take and tolerate at a high therapeutic dose.

Tablet compliance is also a major issue for the treatment of chronic stable angina. In the United Kingdom, this has been reflected in the decreased use of long-term β-blocker therapy for hypertension.3 β-Blockers are cheap and effective in this setting, but are not well tolerated.
The benefits of heart rate reduction in human beings: recent developments

Advances in heart rate reduction - Number 10

Procoralan: clinical evidence

In angina, while β-blockade remains the first-line anti-ischemic agent, Procoralan is proven to be as effective as atenolol, and with a very favorable side effect profile. The International Trial of the Anti-anginal effects of IVabradine compared to atenolol (INITIATIVE) randomized nearly 1000 patients with chronic angina to receive atenolol or Procoralan for 4 months and showed non-inferiority of pure HR lowering with Procoralan. Importantly, benefit was preserved during graded exercise and even suggested improved exercise capacity in the Procoralan group (Figure 5)—perhaps due to improved skeletal muscle and coronary blood flow in those free of widespread adrenergic blockade. These translate into much reduced side effects and improved compliance in patients who may need therapy for many years.

Procoralan has also been compared with non-β-blocking antianginals (ie, amlodipine) and again shown equivalence in a randomized trial of 800 patients. The side effect profile of Procoralan from both of these studies confirms its safety over many hundreds of patient-years of therapy. The main reported side effect of Procoralan is visual, in the form of phosphenes (the brief perception of visual stimuli in the

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**Figure 4.** Chord graph showing the change in left ventricular end-diastolic volumes (LVEDV) for both pacing rate groups (high and low rates being 80 and 60 pulses per minute, respectively) from baseline to follow up assessment at 1 year.

**Figure 5.** Data from the International Trial of the Anti-anginal effects of IVabradine compared to atenolol (INITIATIVE)—a randomized study comparing atenolol with Procoralan in stable angina. Effects on total exercise duration at trough of drug activity. IVA, ivabradine; ATE, atenolol.
absence of a photic challenge). To quote the INITIATIVE investigators "...these symptoms were transient, rated as non-serious, appeared on average after 40 days of treatment, occurred under well-defined conditions, such as light variation, and did not disturb patients' activities. Only five patients withdrew because of visual symptoms."

**Procoralan: forthcoming results**

Key evidence is pending from large-scale trials of pure HR lowering with Procoralan in the coronary artery disease (CAD) and heart failure patients. The morbidity-mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) study is an event-driven, randomized, controlled trial of nearly 10 000 patients with CAD with associated LV dysfunction. Mortality and long-term follow-up data will be available in patients: (i) taking Procoralan in addition to β-blockade; and (ii) in those intolerant of β-blockade at appropriate therapeutic doses. The Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) is an event-driven randomized trial in around 6000 patients with moderate-to-severe chronic heart failure and LV systolic dysfunction. Both these studies will also offer profound mechanistic insights into the role of pure HR lowering in the treatment of CAD and heart failure. The results of BEAUTIFUL are expected in 2008, while those of SHIFT are expected in 2010.

The next 12 months should bring high-quality trial evidence to the fore, opening the next chapter in the pharmacological treatment of CAD as well as heart failure and confirming the efficacy and safety profile of the first new antianginal therapy for 10 years.

**References**

Heart rate reduction is a well-established strategy for ischemia prevention in coronary artery disease (CAD) patients. Heart rate reduction is the primary mechanism by which even β-blockers confer their benefits. Until relatively recently, however, “pure” heart rate slowing has not been possible with drugs approved for use in humans. Available heart rate–slowing drugs (e.g., β-blockers, certain calcium channel blockers) also have other cardioactive properties, such as negative inotropy, peripheral vasomotion, and, that may be beneficial in some patients, but unwanted in others, or may be responsible for adverse effects.

The discovery of the If current and its selective and specific inhibition has provided an opportunity for achieving “pure” heart rate reduction, i.e., heart rate reduction without causing impaired contraction and peripheral effects. The If current has a central role in modulating the rate of spontaneous diastolic depolarization in the sinoatrial node. Procoralan possesses high selectivity and specificity for f-channels, while being devoid of other cardiac effects, and thus has the potential to provide the benefit of heart rate reduction without other, unwanted, cardiovascular actions.

Advantages of “pure” heart rate reduction

Procoralan lowers the heart rate and thus reduces myocardial oxygen consumption. Heart rate reduction with Procoralan is also associated with an increase in diastolic perfusion time, thus improving myocardial oxygen supply. The effects of If current inhibition with Procoralan also differ from the negative inotropy resulting from β-blockade, which increases left ventricular ejection time and thus limits the beneficial increase in diastolic time afforded by heart rate reduction.

Moreover, Procoralan limits exercise-induced tachycardia without altering physiological coronary blood flow, coronary artery diameter, or total peripheral resistance. During exercise, unlike the β-blockers, Procoralan does not induce unmasking of α-adrenergic coronary vasoconstriction. This property of Procoralan contributes to improving oxygen supply through the increased coronary blood flow (Figure 1).

Thus, Procoralan offers the same advantages as β-blockade in terms of heart rate reduction, but not at the expense of impaired ventricular relaxation and unmasking of α-adrenergic coronary vasoconstriction.

Clinical evidence concerning pure heart rate reduction with Procoralan

Procoralan consistently reduces heart rate at rest and during exercise, at both peak and trough of drug activities. Reductions are dose-proportional and parallel to improvements in exercise tolerance and time to development of ischemia. Placebo-subtracted heart rate reduction at rest ranges from an average of approximately 13 bpm at the highest dosage to approximately 3 bpm at the lowest dosage. These reductions are similar in magnitude to those generally expected with therapeutic dosages of β-blocking drugs and greater than usually seen with calcium channel blockers, but without the blood pressure reduction and other functional changes that tend to occur with these other agents. Emerging data confirm a relationship between reduction in heart rate with Procoralan and baseline heart rate. The dependence of rate reduction on baseline conditions implies greatest efficacy in patients with the highest heart rates at baseline, while potentially protecting against the effects of excessive bradycardia (Figure 2).

Efficacy of Procoralan in alleviating angina pectoris

The heart rate reduction associated with Procoralan has been shown to be accompanied by a paralleled effect on angina prevention. Findings from a placebo-controlled trial demonstrated the antianginal efficacy in 360 patients with chronic stable angina.

In the INternational TrIal of the AntTi-anginal effects of IVabradinE compared to atenolol (INITIATIVE) assessing Procoralan 7.5 or 10 mg twice daily vs atenolol 100 mg daily,
the mean number of angina attacks fell by approximately two thirds (reduction of 1.6±4.1 attacks per week with Procoralan 7.5 mg twice daily vs 1.2±3.4 attacks per week with atenolol 100 mg). The improvement in exercise capacity per beat reduction in heart rate was greater with Procoralan than with atenolol, suggesting a greater antianginal efficiency with pure heart rate reduction. In a trial in 1195 patients with chronic stable angina and documented CAD, randomized to Procoralan 7.5 or 10 mg twice daily or amlodipine 10 mg daily for 3 months, angina attacks were decreased by about two thirds, and short-acting nitrate consumption by about 50%, in all treatment groups.12

The efficacy of Procoralan in reducing frequency of residual angina also was assessed in the 1-year safety study: weekly angina attacks were significantly lower at the end of 1 year than immediately prior to therapy (-1.9±4.8 and -1.2±4.1 with Procoralan 5 and 7.5 mg twice daily, respectively).13

| Major ongoing studies with Procoralan |

Heart rate reduction—particularly “pure” heart rate reduction—is beneficial for angina prevention in patients with CAD. The benefits of pure heart rate reduction may extend beyond angina to reduction in myocardial infarction and death, a plausible possibility given the epidemiologic relationship between heart rate and such outcome events. However, proof of this therapeutic benefit awaits results of trials now ongoing to test the underlying hypothesis. These include the BEAUTIFUL trial (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), to which 10 500 patients with CAD and moderate-to-severe left ventricular dysfunction have now been randomized and will be followed through 2008,14 and the SHIfT trial (Systolic Heart failure treatment with the If inhibitor ivabradine Trial), to which 5500 patients with heart failure and systolic left ventricular dysfunction (three fourths with CAD) are now being randomized.

Figure 2. Heart rate reduction according to baseline heart rate.12

<table>
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<tr>
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References
**What can an \( I_f \) inhibitor contribute to the treatment of coronary patients?**

**Professor Jose Lopez-Sendon**  
Cardiology department. Planta 1.  
Hospital Universitario La Paz Madrid, Spain.

**What types of CAD patients do you see in your practice?**

I am a clinical cardiologist and I am directly involved in the management of patients with both acute and chronic heart diseases. The majority of my patients present with ischemic heart disease, the main complaint is angina and a significant proportion also present with heart failure. In fact, acute and chronic ischemic heart disease represents the main challenge for the cardiologist, because of its high prevalence and chronic nature.

**What are the main objectives in the treatment of this population?**

In ischemic heart disease patients there are three main objectives for treatment: control symptoms, prevent disease progression and improve the short- and long-term outcome. Control of ischemic symptoms implies the reduction of the number of ischemic episodes, improving functional capacity and allowing a normal life. The first step towards this goal is the control of factors associated with an increase in myocardial oxygen consumption: hypertension and increased heart rate or associated with a decrease in oxygen supply such as hypotension, and anemia (Figure 1). Medications effective for reducing ischemia and improving functional capacity include \( \beta \)-blockers, calcium channel blockers, nitrates and late sodium current inhibitors. \( \beta \)-blockers are usually the first choice, but some of the other drugs should be used in case of intolerance or if the symptoms are not fully controlled. Coronary artery revascularization is indicated when control of angina is insufficient as well as in high-risk patients. Secondary prevention plays a very important role in patients with ischemic heart disease, and is usually linked to an improvement in long term outcome and I strongly recommend following the secondary prevention guidelines, with an emphasis on complete smoking cessation, regular exercise and a healthy diet of the Mediterranean type. In addition, I routinely prescribe aspirin and statins to all my patients and angiotensin converting enzyme inhibitors in all patients except the very low risk groups. In patients with heart failure I also follow the guidelines of the European Society of Cardiology. As a routine, I prescribe \( \beta \)-blockers, angiotensin converting enzyme inhibitors (ACE) and aldosterone blockers for all my heart failure patients.

**What do you think about the importance of heart rate reduction in CAD?**

There is a strong relationship between heart rate and cardiovascular disease (Figure 2). Resting heart rate is directly related to ischemic episodes, sudden death, cardiovascular mortality and all cause mortality in patients with known ischaemic heart disease as well as in the healthy population (Figure 3). The detrimental effects of heart rate increase include an increase in myocardial oxygen demands, a reduction of diastole and oxygen supply to the myocardium, a decrease in the fibrillation threshold and plaque rupture.

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**Figure 1.** Myocardial ischemia is the consequence of a imbalance between myocardial oxygen supply and consumption.
Also, heart rate is associated with a number of other risk factors such as hypertension, diabetes and poor fitness. Although heart rate is one of the most readily accessible clinical variables and a high heart rate is perceived as undesirable, the prognostic value of heart rate remains poorly appreciated and very often is not even considered requiring monitoring or treatment in clinical practice. There is growing evidence that reduction of heart rate is linked with an improvement in ischemic symptoms in patients with angina and may also be related to an improvement in prognosis in patients with acute or chronic heart disease and heart failure.2

Exercise training, β-blockers and some calcium channel blockers reduce resting heart rate and the clinical benefit of these therapies is, at least in part, related to the reduction in heart rate. However, a significant number of patients present contraindications for the use of verapamil or diltiazem (heart failure, AV conduction abnormalities, hypotension) or β-blockers (asthma, hypotension), and complications due to secondary effects, especially hypotension, may mean these drugs can not be used in appropriate doses to obtain the desirable reduction in heart rate.

Procoralan is a novel drug recently approved in Europe for the treatment of patients with stable coronary artery disease and angina. Procoralan reduces heart rate by a unique mechanism. Blocking the f channels in the sinus node cell membrane delays the diastolic depolarization of the sinus node thus reducing heart rate without effect on myocardial contractility, AV conduction or vascular effects. This option opens new therapeutic opportunities for the treatment of myocardial ischemia, heart failure, secondary prevention of cardiovascular diseases, and maybe to reduce the risk associated with sinus tachycardia in the healthy population.2 In several studies in patients with chronic stable angina, Procoralan was superior to placebo in controlling the episodes of angina and improving functional capacity. In other studies, Procoralan was equally effective to atenolol and amiodipine to reduce ischemia, control angina and improve functional capacity and provides an extra clinical benefit when combined with classical antianginal drugs such as nitrates or calcium channel blockers.2 These findings in well conducted clinical trials were the basis for its recommendation in patients with stable chronic angina in the European Society of Cardiology guidelines.1

Procoralan is easy to use and has a good safety profile.3 It is well tolerated in chronic treatment, excessive heart rate
reduction is very rare and visual symptoms (usually transient) enhance brightness or phosphenes—commonly associated with abrupt changes in light intensity—is the major complaint, causing the withdrawal of Procoralan in about 1% of patients. I usually start treatment with 5 mg twice a day and increase the dose to 7.5 mg if the desirable reduction in heart rate is not achieved. Procoralan use is contraindicated in combination with strong CYP 3A4 inhibitors but could be safely used in combination with common cardiovascular therapies including ACE-inhibitors, angiotensin and anti-aldosterone blockers, nitrates, statins, warfarin, sildenafil, aspirin and other anti-platelet agents. Combination with β-blockers, can be considered if a further reduction in heart rate is desired.

Several ongoing morbidity-mortality trials further explore the clinical benefits of If inhibition. The BEAUTIFUL trial is investigating the morbidity-mortality benefits of ivabradine on top of other medications in CAD patients, while the SHIFT trial is designed to investigate the morbidity-mortality benefits of Procoralan on top of other medications in HF patients. The results of these trials will provide important information in defining new applications of this drug.

References
New solution for angina patients needing a new therapeutic approach

Procoralan®

The first selective and specific \( I_f \) inhibitor

Presentation and composition: Procoralan 5 mg: film-coated, scored tablet; Procoralan 7.5 mg: film-coated tablet. Indication: Symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contraindication or intolerance for \( \beta \)-blockers. Dosage and administration: The starting dose is 5 mg orally twice daily, during meals: breakfast and dinner. The dose can be increased to 7.5 mg twice daily after 1 month of treatment, depending on the therapeutic response. If heart rate decreases persistently below 50 beats per minute (bpm) at rest, treatment should be downtitrated to 2.5 mg twice daily. Properties: Procoralan is a pure heart rate–lowering agent, acting by a selective inhibition of the cardiac pacemaker \( I_f \) current that controls spontaneous depolarization in the sinus node and regulates heart rate. Procoralan dose-dependently reduces heart rate and provides significant anti-ischemic and antianginal efficacy. Contraindications: Hypersensitivity to Procoralan, resting heart rate below 60 bpm prior to treatment, cardiogenic shock, acute myocardial infarction, severe hypotension, sinoatrial block, third-degree AV block, severe heart failure (NYHA class III-IV), severe hepatic insufficiency (in the absence of data), pregnancy and lactation (in the absence of data), coadministration with a strong CYP 3A4 inhibitor. Interactions: Combination with heart rate–reducing agents, combination with QT-prolonging medicinal products, CYP 3A4 inhibitors and inducers. Precautions: Use with caution in patients with severe renal insufficiency (creatinine clearance <15 mL/min), use with caution in patients with second-degree AV-block, with cardiac arrhythmias, or stroke. Side effects: Phosphenes, bradycardia, ventricular extrasystoles, headache. Presentation: Pack of 56 tablets of Procoralan 5 mg, Pack of 56 tablets of Procoralan 7.5 mg. Please refer to the complete summary of product characteristics for your country, as country-specific variations may exist.


1 tablet twice daily