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Expediente No.: **06 127 373**
Asunto: **Contestación de requerimiento de fondo de la Patente de
Invención: "Nueva Composición de un Inhibidor de la
corriente sinusal If y de un inhibidor cálcico y las
composiciones farmacéuticas que lo contienen".**
Solicitante: **LES LABORATOIRES SERVIER**

JULIO CÉSAR RAMÍREZ PIÑA, abogado en ejercicio, identificado con la cédula de ciudadanía número 79'779.990 de Bogotá, portador de la tarjeta profesional número 113.206 del C. S. de la J., domiciliado en esta ciudad en la carrera 11 No. 86 - 32 (oficina 101) de Bogotá, D.C., en mi condición de apoderado de la sociedad **LES LABORATOIRES SERVIER**, tal y como consta en el poder que obra en el expediente radicado el pasado 22 de octubre de 2009, por medio del presente escrito doy respuesta al requerimiento de fondo que obra en el Oficio 005011 notificado mediante fijación en lista del 15 de abril de 2010, en virtud de lo cual apporto los siguientes documentos:

1. TARDIF J-C: "Ivabradine in clinical practice: Benefits of (f) inhibition." European Heart Journal Supplement, vol. 7, No. H. Pp H29-H32.Refs.: 26 ISSN: 1520-765X, Coden: EHJSFT, 2005.
2. Lopez-BESCOS ET AL: "Long term safety and antianginal efficacy of the If current inhibitor ivabradine." Eur. Heart J. Vol. 25 (Supl), 2004, p. 138.
3. RUZYLLO ET AL: "Antianginal and antiischemic effects of the If current inhibitor ivabradine." Eur. Heart J. Vol. 25 (Supl), 2004, p. 138.

I. ANEXOS

Se adjuntan los documentos antes mencionados en 5 folios.



Ivabradine in clinical practice: benefits of I_f inhibition

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KEYWORDS

Angina
Heart rate
Pharmacology

Relieving the symptoms of angina and improving the quality of life and functional status are important objectives in the management of patients with chronic stable angina. A high heart rate induces or exacerbates myocardial ischaemia and angina, because it both increases oxygen demand and decreases myocardial perfusion, the latter by shortening the duration of diastole. Moreover, there is a large body of evidence about the relationship between high resting heart rate and mortality, documented in different population types. β -Blockers are effective in reducing angina largely by decreasing heart rate. Physician use and patient compliance may be limited by the side effects of β -blockers, which include fatigue, depression, and sexual dysfunction. Heart rate reduction can also be obtained by some calcium antagonists and by the new agent ivabradine. Ivabradine (Procoralan) is a selective and specific I_f inhibitor, which acts on one of the most important ionic currents for the regulation of the pacemaker activity of sinoatrial node cells. Ivabradine has demonstrated dose-dependent anti-ischaemic and anti-anginal effects at dosages of 5, 7.5, and 10 mg bid in an extensive programme of more than 5000 patients. The non-inferiority of ivabradine was shown vs. the β -blocker atenolol and the calcium-channel blocker amlodipine. Unlike β -blockers, ivabradine is devoid of intrinsic negative inotropic effects and does not affect coronary vasomotion. A whole range of patients with angina may benefit from exclusive heart rate reduction with ivabradine, including those with contraindications or intolerance to the use of β -blockers and patients who are insufficiently controlled by β -blockers or calcium-channel blockers.

Introduction

Chronic stable angina is a common and disabling condition, affecting 30 000–40 000 per 1 million people in Europe and the United States. Angina results when myocardial perfusion is insufficient to meet metabolic demand. Individuals with typical chronic stable angina usually have significant narrowing of at least one major epicardial vessel and experience pain, which is related to an increase in physical activity or psychological stress. Heart rate is one of the most important determinants of myocardial oxygen demand. A high heart rate

induces or exacerbates myocardial ischaemia and subsequent angina, because it both increases myocardial oxygen demand and decreases myocardial perfusion, the latter by shortening the duration of diastole.

Relieving the symptoms of angina and improving the quality of life and functional status are an integral part of the management of patients with chronic stable angina.¹ β -Blockers are effective in reducing angina largely by decreasing the heart rate² and they have been usually preferred as initial therapy in the absence of contraindications.³ Despite the demonstrated safety and effectiveness of β -blockers, physician use and patient compliance may be somewhat limited by the side effects of this class of agents, which include fatigue, sexual dysfunction, depression, cold extremities, light-headedness, gastrointestinal disturbances,

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bronchospasm, and atrioventricular (AV) block.^{4,5} β -Blockade can also increase coronary resistance and limit the exercise-induced increase in coronary arterial flow.^{6,7} In addition, β -blockers can reduce left ventricular contractility and have negative lusitropic effects.⁸ Finally, this class of agents can have detrimental effects on carbohydrate and lipid metabolism.^{9,10}

Prognostic value of heart rate in patients with coronary artery disease

Resting heart rate has been shown to be associated with mortality in patients with hypertension as well as those with the metabolic syndrome.¹¹ We have recently evaluated the relationship between resting heart rate and future cardiovascular events in a population of 25 000 patients with suspected or proven coronary artery disease (CAD).¹¹ Over a median follow-up of 14.7 years, resting heart rate was a predictor of overall and cardiovascular mortality, independent of other known risk factors such as hypertension, diabetes, and smoking. The size of the study also allowed adjustment of the multivariable model for the extent of CAD and left ventricular ejection fraction. Resting heart rate was an independent risk factor for total and cardiovascular mortality, even after adjusting for such covariates. A high resting heart rate (≥ 83 beats per minute (b.p.m.)) was indeed a strong predictor of total and cardiovascular mortality (hazard ratios of 1.32 and 1.31, respectively). In addition, resting heart rate was a risk factor for time to cardiovascular rehospitalizations.

Pharmacological properties of the I_f inhibitor ivabradine

I_f , a mixed Na^+ - K^+ inward current activated by hyperpolarization and modulated by the autonomic nervous system, is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial node. Ivabradine (Procoralan®) is a novel, specific heart rate-lowering agent, which acts in sinoatrial node cells by selectively and specifically inhibiting the pacemaker I_f current in a dose-dependent manner.^{12,13} It slows the diastolic depolarization slope of the action potential of sinoatrial node cells¹⁴ and reduces heart rate at rest and during exercise in animals¹⁴⁻¹⁷ and human volunteers.¹⁸ Ivabradine has demonstrated anti-ischaemic and anti-anginal activities at doses of 5 and 10 mg bid in a placebo-controlled study involving 360 patients with stable angina.¹⁹

Ivabradine is devoid of intrinsic inotropic effects and does not affect either the left ventricular systolic function or coronary vasomotion in experimental models at rest and during exercise.^{8,20} Ivabradine has no detectable effect on AV node cells, as evidenced by the absence of change in PR interval or any other intraventricular conduction parameters.²¹ An intravenous dose

of ivabradine does not prolong the corrected QT interval or modify conductivity and refractoriness of the atria, AV node, His-Purkinje system, and ventricles.²¹ In addition, Manz et al.²² studied with echocardiography the impact of a single intravenous dose of ivabradine on left ventricular function in patients with systolic dysfunction. The left ventricular ejection fraction did not decrease significantly with ivabradine (0.2%) when compared with placebo (1.7%). Other echocardiographic parameters, such as fractional shortening and stroke volume, were also unchanged after the intravenous administration of ivabradine. Left ventricular relaxation is as crucial for optimal left ventricular function as is contractility. The negative lusitropic effect of β -blockers could therefore be potentially deleterious. Colin et al.²³ investigated the effects of ivabradine and atenolol on left ventricular isovolumetric relaxation at rest and during treadmill exercise in chronically instrumented dogs. For a similar reduction in heart rate at rest and during exercise, ivabradine, in contrast to atenolol, did not exert any negative lusitropic effect. In addition, in contrast to β -blockers, ivabradine does not cause detrimental effects on coronary vasomotion.⁸

Ivabradine vs. β -blockers in stable angina

In the International Trial of the Anti-anginal effects of Ivabradine compared to atenolol (INITIATIVE), a 4-month randomized, double-blind, controlled multicentre study of 939 patients with stable angina, the non-inferiority of ivabradine, 7.5 and 10 mg bid, compared with atenolol, 100 mg once daily, in terms of their anti-anginal and anti-ischaemic effects was demonstrated for all exercise parameters.²⁴ Ivabradine increased total exercise duration by ~1.5 min at the trough of drug activity, and times to limiting angina and angina onset were also improved. The increase in time to 1 mm ST-segment depression indicates that the improvement in total exercise capacity is associated with a relevant anti-ischaemic effect of ivabradine.

Ivabradine vs. calcium-channel blockers in angina

A large clinical trial was also conducted to demonstrate the non-inferiority of ivabradine vs. the calcium-channel blocker amlodipine. Ivabradine at doses of 7.5 and 10 mg bid was compared with amlodipine 10 mg once daily during 3 months of therapy in a randomized trial that involved 1195 patients with chronic stable angina and documented CAD.²⁵ In that study, ivabradine 7.5 mg bid was found to have efficacy indistinguishable from that of amlodipine 10 mg once daily for all measured bicycle exercise test parameters. Statistical testing also revealed that ivabradine is non-inferior to amlodipine ($P < 0.0001$) in preventing angina attacks.

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Combination anti-anginal therapy

Considerable evidence suggests that combination therapy may be more effective than monotherapy for the treatment of angina pectoris.¹³ The efficacy and safety of combination therapy with ivabradine have been established over 1 year in 386 patients with stable angina already treated by nitrates or dihydropyridine calcium-channel blockers.¹⁴ Two different dosages of ivabradine were used: 5 and 7.5 mg bid. Ivabradine was shown to reduce the heart rate of patients by 10 b.p.m. at 5 mg bid and 12 b.p.m. at 7.5 mg bid. Ivabradine maintained this heart rate reduction over the year of follow-up. The number of angina attacks reported by patients was reduced significantly by the addition of ivabradine.

Tolerability of ivabradine

Ivabradine has demonstrated a very good safety profile throughout its large clinical development programme. More than 5000 patients have been included in this clinical programme, with 3500 patients treated with ivabradine and 1200 of these patients treated for >1 year. The most frequent adverse drug reactions have been visual symptoms, the majority being phosphenes that were transient and non-serious in nature. These symptoms consisted of transient enhanced brightness in limited areas of the visual field that were commonly associated with abrupt changes in light intensity. The visual symptoms were dose dependent and generally mild and well tolerated, causing <1% of patients to withdraw from treatment. They may be related to the action of ivabradine at HCN (hyperpolarization-activated, cyclic nucleotide-gated cation currents) channels known to be present in the retina. All visual symptoms resolved spontaneously during therapy or after drug discontinuation. Importantly, the abrupt discontinuation of ivabradine has not resulted in a rebound angina phenomenon. In summary, the clinical tolerability of ivabradine was documented in a large population of patients with CAD and stable angina, and drug-related adverse events had minimal impact on acceptability.

Patient profiles

Ivabradine shares with β -blockers the property of decreasing heart rate and oxygen demand from the ischaemic heart, which is presumably fundamentally important in mediating anti-ischaemic effects. In the light of the positive results obtained in clinical trials, the place of ivabradine in the therapeutic armamentarium must be considered (Table 1). Given the absence of cardiac effects other than exclusive heart rate lowering, ivabradine is probably suitable for most patients with stable angina and is of particular interest in patients in whom β -blockers should be avoided (those with AV block, peripheral vascular disease, and obstructive pulmonary disease) and in those who do not tolerate well β -blockers or calcium antagonists. Unlike β -blockers,

Table 1 Advantages of ivabradine in patients with angina

Exclusive heart rate reduction
Proven anti-ischaemic and anti-anginal properties
Absence of negative inotropic effects
Preservation of left ventricular relaxation (lack of effects on diastolic function)
Absence of coronary vasoconstriction
Preserved atrioventricular and ventricular conduction
Preservation of blood pressure
Absence of bronchospasm associated with β -blockers

ivabradine may be used in vasospastic angina because it does not increase coronary vasomotor tone.

In addition to the side effects of β -blockers, which include depression, fatigue, and cold extremities, erectile dysfunction is a particularly important problem associated with their use in middle-aged men. Ivabradine may therefore be very useful in such patients. Although asthma or chronic obstructive pulmonary disease (COPD) represents only relative contraindications to β -blockade, some patients clearly develop bronchospasm and wheezing with β -blockers, which require dose reduction or abrupt withdrawal. Such patients who require heart rate reduction would clearly benefit from the lack of this side effect with ivabradine. Furthermore, some patients with both CAD and COPD develop angina when treated with inhaled β -adrenergic agonists because of the resulting tachycardia. The heart rate reduction obtained with ivabradine could also be very helpful in this setting. Patients with CAD can have variable degrees of AV block that develop or are exacerbated with β -blockers. The need for selective heart rate reduction in patients with myocardial ischaemia and AV node conduction abnormalities represents another excellent indication for ivabradine. This is particularly relevant for older patients with a prolonged PR interval.

Conclusion

Heart rate slowing is an integral part of an optimal pharmacological anti-anginal strategy. β -Blockers have been considered traditionally as a first-line therapy for stable angina, but their use may be limited by side effects including fatigue, depression, and sexual dysfunction. Bronchospasm and AV block represent other limitations of β -blockers. Ivabradine is a selective and specific I_f inhibitor with anti-anginal and anti-ischaemic effects that have been shown to be non-inferior to those of the β -blocker atenolol and the calcium-channel blocker amlodipine. Unlike β -blockers, ivabradine is devoid of intrinsic negative inotropic effects and does not affect coronary vasomotion. A whole range of patients with angina may benefit from exclusive heart rate reduction with ivabradine, including those with contraindications or intolerance to the use of β -blockers and patients who are insufficiently controlled by β -blockers or calcium-channel blockers.

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function (BNP: 918 ± 604 pg/ml). The optimal BNP cut-off level, identified by receiver operating characteristic analysis (AUC 0.95), was >80 pg/ml with a sensitivity of 64% and a specificity of 91%, with a net saving of 31% of total costs, without compromising the diagnostic accuracy.

ROC analysis/BNP cut-off

BNP (pg/ml) (study group %)	Sensitivity %	Specificity %
30 (24%)	69	71
50 (32%)	83	85
70 (38%)	87	89
90 (40%)	84	90
100 (43%)	89	91
120 (46%)	78	92

Conclusions: Blood BNP concentrations, in patients with symptoms suspected by a general practitioner, can play an important role for diagnosing and stratifying pts into risk groups of cardiac dysfunction.

NOVEL THERAPEUTIC STRATEGIES IN CHRONIC STABLE ANGINA

876 Long-term safety and antianginal efficacy of the If current inhibitor ivabradine in patients with chronic stable angina. A one-year randomised, double-blind, multicentre trial

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Background: Ivabradine, is a novel selective and specific inhibitor of the If current in the sinus node. Previous reports demonstrated anti-ischaemic and anti-anginal effects similar to the beta blocker atenolol. The objective of the present study was to assess the long-term safety and antianginal efficacy of two doses of ivabradine. **Methods:** 388 patients with a ≥ 3 -month history of chronic stable angina and documented CAD were randomised double-blind to two parallel-groups receiving either ivabradine 5 mg bid (n=198, group 1) or ivabradine 7.5 mg bid (n=190, group 2) for twelve months. Concomitant medication including AAS, serum lipid lowering agents, long acting nitrates or dihydropyridine calcium channel blockers were authorised during the study. Safety was assessed on reported adverse events in follow-up visits at 1, 3, 6, 9 and 12 months. Mean treatment time on the study drug was 10.4 ± 3.6 months/pat. Antianginal efficacy was based on the reduction in the number of angina attacks per week reported in patients diary from M0 to M12.

Results: ivabradine was safe and well tolerated throughout the study duration. Transient visual symptoms, (phosphenes like), mostly of mild intensity where the most frequently reported adverse events, but lead to treatment withdrawal in only 4 patients (1 in group 1, and 3 in group 2).

Resting heart rate was reduced 10 bpm in group 1 (from 71 to 62 bpm) and 12 bpm in group 2 (71 to 59 bpm) at the end of treatment. Only in 3 cases (0.8%, all from group 2) sinus bradycardia was the cause of treatment withdrawal. At M12 uncorrected QT was increased consistently with the reduction in heart rate while corrected QT (QTc) was unchanged. No ECG abnormality was detected in this study.

The number of angina attacks per week showed a significant reduction at M12 as compared to M0: -1.9 ± 0.4 (95%CI [-2.6; -1.3]) and -1.2 ± 0.4 (95%CI [-1.9; -0.5]) with ivabradine 5 and 7.5 mg bid, respectively.

Conclusion: In this one-year double-blind trial ivabradine was shown to be safe and well tolerated at the usual recommended doses of 5 and 7.5 mg bid for the treatment of stable angina. Both doses of ivabradine demonstrated relevant anti-anginal efficacy in patients with documented CAD and chronic stable angina stable angina treated with concomitant anti-anginal medications.

877 A randomized, double-blind, placebo-controlled, Phase 2 study: the efficacy of fasudil in patients with stable angina

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Background: Fasudil, an orally available rho-kinase inhibitor, selectively inhibits coronary arterial vasoconstriction and may modify other processes causing myocardial ischaemia.

Objective: To evaluate the effectiveness of fasudil in the treatment of stable angina. Favourable safety and tolerability are reported separately.

Methods: In a Phase 2, multicentre, double-blind, placebo-controlled, randomized trial, the effects of fasudil were evaluated on total exercise duration, time to onset of myocardial ischaemia (≥ 1 mm ST-segment change), Canadian Cardiovascular Society (CCS) class and quality of life measures in patients with stable angina. Patients with objective evidence of coronary artery disease were required to have reproducible baseline exercise test times and exercise-induced ST segment depression ≥ 1 mm. A total of 84 of the 208 patients screened met entry criteria and were randomized 1:1 to placebo or fasudil. Anti-anginal medications were limited to nitroglycerin prn and monotherapy with either a beta- or calcium-channel blocker. Other cardiovascular medications including aspirin, statins and ACE inhibitors were allowed. After a 3-week washout period, fasudil or matching placebo was force-titrated from 20 mg tid to 80 mg tid with 20 mg tid increments every 2 weeks. Final efficacy measures were obtained after 8 weeks.

Results: At study end, exercise duration 1 hour post-dosing was increased by 1.97 min (118.4 sec) in the fasudil group and by 1.43 min (86.1 sec) in the placebo group (both $p < 0.001$ vs baseline but $p = ns$ between groups). Time to onset of myocardial ischaemia was increased by 2.87 min (172.1 sec) in the fasudil group and by 0.73 min (43 sec) in the placebo group (RR=0.45, $p=0.012$). The percentage of patients with ≥ 1 CCS class improvement showed a positive fasudil dose-dependent trend ($p = ns$). No significant differences between groups in the weekly frequency of angina attacks or use of nitroglycerin were observed, but positive trends in the physical limitation and treatment satisfaction scores of the modified Seattle Angina Questionnaire (SAQ) were observed with fasudil treatment.

Conclusions: This Phase 2 dose-finding trial demonstrated that titrating fasudil to 80 mg tid over 8 weeks improved time to exercise-induced myocardial ischaemia compared to placebo in stable angina patients. Favourable trends in exercise time, CCS class and SAQ scores were also observed. Thus, fasudil is promising as a new therapy for myocardial ischaemia.

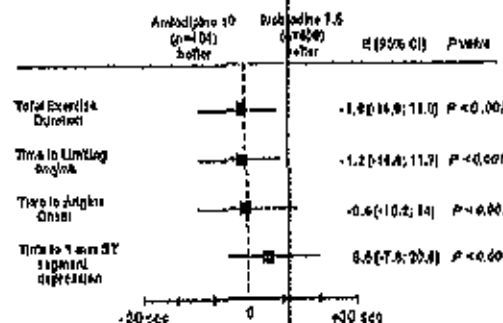
878 Antianginal and antiischaemic effects of the If current inhibitor ivabradine compared to amlodipine as monotherapies in patients with chronic stable angina. Randomised, controlled, double-blind trial

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Background: Ivabradine, a novel selective and specific inhibitor of the If current in the sinus node, has previously demonstrated anti-ischaemic and anti-anginal activity in a placebo-controlled trial (Borer 2003) and similar anti-anginal efficacy than the beta-blocker atenolol (Tardif 2003). The objective of this study was to demonstrate the non-inferiority of the anti-anginal and anti-ischaemic effects of ivabradine (Iv) compared to amlodipine (Am).

Methods: In a double-blind, parallel-group, non-inferiority trial (equivalence limits of 30 sec on total exercise duration), 1165 patients with a ≥ 3 -month history of chronic stable angina and documented CAD were randomised to three groups receiving Iv 7.5 mg bid (n=400), Iv 10 mg bid (n=391) and Am 10 mg od (n=404) for three months. Patients underwent bicycle exercise tolerance tests (ETT) at randomisation (M0) and every month until the third month (M3).

Results: Total exercise duration at trough (primary endpoint) was increased from M0 to M3 by 27.6 ± 91.7 sec, 21.7 ± 84.6 sec with Iv 7.5 and 10 mg bid, respectively and by 31.2 ± 92.0 sec with Am 10 mg od confirming the non inferiority of Iv vs Am ($p < 0.001$). Time to limiting angina, time to angina onset and time to 1 mm ST segment depression were also consistently increased. In contrast, heart rate and rate pressure product were significantly more reduced with ivabradine than with amlodipine at rest and at peak exercise.



The number of angina attacks were decreased by about two thirds and the short acting nitrates consumption by about one half across the study in all treatment groups.

Conclusion: In this large 3-month double-blind controlled trial, treatment with ivabradine was shown to be as effective and safe as amlodipine in patients with chronic stable angina.