(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 2404600 B1**

(19) NO

NORGE

(51) Int Cl.

A61K 31/4045 (2006.01)
A61K 31/55 (2006.01)
A61K 45/06 (2006.01)
A61P 9/04 (2006.01)

Patentstyret

(21)	Oversettelse publisert	2015.11.02
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2015.05.27
(86)	Europeisk søknadsnr	11290269.7
(86)	Europeisk innleveringsdag	2011.06.14
(87)	Den europeiske søknadens Publiseringsdato	2012.01.11
(30)	Prioritet	2010.06.15, FR, 1002525
(84)	Utpekte stater	AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
	Utpekte samarbeidende stater	BA ME
(73)	Innehaver	Les Laboratoires Servier, 35, rue de Verdun, 92284 Suresnes Cedex, FR-Frankrike
(72)	Oppfinner	Thuillez, Christian, 30, rue Louis Bouilhet, 76000 Rouen, FR-Frankrike Mulder, Paulus, 15, Chemin du Mont à Cat, 76130 Mont Saint Aignan, FR-Frankrike Vilaine, Jean-Paul, 21, rue des Vallées, 92290 Chatenay Malabry, FR-Frankrike Fratacci, Marie-Dominique, 69, avenue Paul-Vaillant Couturier, 78390 Bois d'Arcy, FR-Frankrike Lerebours-Pigeonniere, Guy, 28, avenue de l'Europe, 92300 Levallois-Perret, FR-Frankrike Feldmann, Luc, 22, rue Tocqueville, 75017 Paris, FR-Frankrike Roussel, Jérôme, 20, rue Pasteur, 78220 Viroflay, FR-Frankrike
(74)	Fullmektig	Oslo Patentkontor AS, Postboks 7007 Majorstua , 0306 OSLO, Norge

(54) Benevnelse **Use of the combination of a sinus current If inhibitor and an inhibitor of the angiotensin conversion enzyme for treating cardiac insufficiency with preserved systolic function**

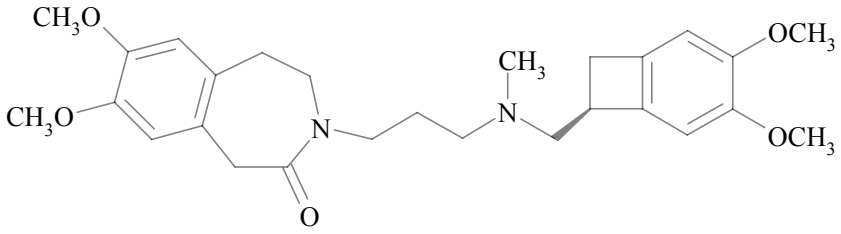
(56) Anførte publikasjoner

EP-A1- 1 354 873
EP-A1- 1 362 590
EP-A1- 2 036 892
EP-A1- 2 039 682
WO-A2-01/78699
RU-C1- 2 364 401

Description

The present invention relates to the use of the association of:

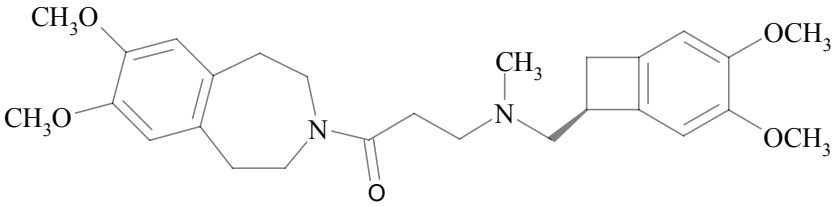
- ivabradine, or 3-{3-[{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one, of formula (I):



(I),

and its addition salts with a pharmaceutically acid, their hydrates and crystalline forms, or

- *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine of formula (II)



(II),

and its addition salts with a pharmaceutically acid, their hydrates and crystalline forms,

with perindopril, or one of its addition salts with a pharmaceutically acceptable base, their hydrates or crystalline forms,
in obtaining medicaments intended for the treatment of heart failure with preserved systolic function.

Ivabradine, and its addition salts with a pharmaceutically acceptable acid, and more especially its hydrochloride, their hydrates and crystalline forms, and *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine, and its addition salts with a pharmaceutically acceptable acid, and more especially its hydrochloride

and its fumarate, their hydrates and crystalline forms, are selective and specific sinus node I_f current inhibitors and have very valuable pharmacological and therapeutic properties, especially negative chronotropic (heart-rate-reducing) properties, making those compounds useful in treating, preventing and improving the prognosis of various cardiovascular diseases associated with myocardial ischaemia such as angina pectoris, myocardial infarction and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in chronic heart failure.

The preparation and therapeutic use of ivabradine and its addition salts with a pharmaceutically acceptable acid, more especially its hydrochloride, have been described in European patent specification EP 0 534 859.

The preparation and therapeutic use of *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine and its addition salts with a pharmaceutically acceptable acid, and more especially its hydrochloride and its fumarate, have been described in European patent specification EP 2 036 892.

Perindopril is an angiotensin-converting enzyme inhibitor.
Angiotensin-converting enzyme inhibitors are one of the major therapeutic classes in the treatment of arterial hypertension. They act principally by inhibiting the synthesis of angiotensin II and by blocking the breakdown of bradykinin.
In addition to the lowering of arterial pressure, they have been shown to improve the morbidity (myocardial infarction, cerebral vascular accidents) and cardiovascular mortality of hypertensive patients, diabetic patients and patients with pre-existing coronary disease.

Amongst the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid, camphoric acid, pamoic acid and 1,5-naphthalenedisulphonic acid.

The Applicant has discovered that the association of:

- ivabradine, or 3-{3-[{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one, or
- *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine,

and perindopril has valuable properties allowing its use in the treatment of heart failure with preserved systolic function.

Heart failure due to systolic dysfunction of the left ventricle is not the only form of heart failure. Increasingly often, patients with heart failure have an ejection fraction which is greater than 40 %. The proportion of heart failure referred to as "diastolic heart failure" (or rather "heart failure with preserved systolic function") increases with age. It currently accounts for 30 to 40 % of hospital admissions for heart failure and, after the age of 80, its frequency exceeds that of heart failures due to systolic dysfunction. Diastolic heart failures generally feature both prolonged ventricular relaxation and a reduction in the distensibility of the left ventricle chamber. The basic causes are ischaemic, hypertensive and elderly-patient cardiopathies. Predisposing factors are age, sex (female), diabetes, obesity and arterial hypertension. Concentric remodelling of the left ventricle, with or without hypertrophy, consistently gives rise to disruption of diastolic function. In most cases a triggering factor is found to be the cause of a congestive attack. The frequency of "diastolic" heart failure increases with age. Its physiopathology remains complex and merits being better understood by clinicians.
No treatment has hitherto demonstrated efficacy in this pathology, the mortality (50 % at 4 years) of which corresponds to that of systolic heart failure.

The Applicant has discovered that the use of the association of ivabradine or *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine and perindopril makes it possible to obtain pharmacological effects that are superior to those observed when using either ivabradine or *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine on their own or perindopril on its own. The use of the association of ivabradine or *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine and perindopril

moreover makes it possible for the observed physiological parameters to return to values very close to normal. These observations make it possible to envisage using the association of ivabradine or *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine and perindopril in the treatment of heart failure having preserved systolic function.

Perindopril is used as such or in the form of one of its addition salts with a pharmaceutically acceptable acid or base, and more especially its *tert*-butylamine or arginine salts, their hydrates and crystalline forms.

The present invention relates also to pharmaceutical compositions comprising as active ingredients:

- ivabradine, or one of its hydrates, crystalline forms, and addition salts with a pharmaceutically acceptable acid and more especially its hydrochloride, or *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine or one of its addition salts with a pharmaceutically acceptable acid, and more especially its hydrochloride and its fumarate, their hydrates or crystalline forms, and
- perindopril, or one of its addition salts with a pharmaceutically acceptable base, and more especially its *tert*-butylamine or arginine salts, their hydrates or crystalline forms,

for use in the treatment of heart failure with preserved systolic function.
The pharmaceutical compositions that may be used are those that are suitable for oral, parenteral or nasal administration, tablets, dragées, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels etc. and also pharmaceutical compositions having programmed, delayed, prolonged or deferred release.

Besides ivabradine or *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine and perindopril, said pharmaceutical compositions comprise one or more excipients or carriers selected from diluents, lubricants, binders, disintegration agents, absorbents, colourants, sweeteners etc.

By way of non-limiting example there may be mentioned:

- *as diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerol,
- *as lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol,
- *as binders*: magnesium aluminium silicate, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone,
- *as disintegrants*: agar, alginic acid and its sodium salt, effervescent mixtures.

The useful dosage varies according to the sex, age and weight of the patient, the administration route, the nature of the disorder and of any associated treatments and ranges from 2.5 to 30 mg of ivabradine per 24 hours, and more preferably from 5 to 15 mg per day, and even more preferably from 10 to 15 mg per day. The dose of N-{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-N-methyl-3-oxo-1-propanamine (hereinafter referred to as compound A) may vary from 5 to 100 mg per day. The dose of perindopril may be less than that used when it is administered on its own.
The daily dose of perindopril will preferably be between 1 and 10 mg inclusive.

The Examples that follow illustrate the invention.

List of abbreviations used

dP/dt_{max}	:	maximum increase in pressure per second
dP/dt_{min}	:	maximum reduction in pressure per second
HF	:	heart failure
LVEDP	:	Left Ventricular End Diastolic Pressure
LVEDPVR	:	Left Ventricular End Diastolic Pressure Volume Relation
LVESP	:	Left Ventricular End Systolic Pressure
LVESPVR	:	Left Ventricular End Systolic Pressure Volume Relation
LV	:	left ventricle

Pharmacological tests:

Heart failure is induced in rats by ligature of the left coronary artery (the control animals undergo an operation but are not ligated), which causes ischaemia of part of the wall of the left ventricle. The animals recuperate for 7 days and then, for 12

weeks, they are given either 3 mg/kg of compound A, or 0.4 mg/kg of perindopril, or perindopril and compound A concomitantly.
Twelve weeks after the operation it is found that the animals having undergone coronary ligature develop heart failure that is both systolic (ejection anomaly) and diastolic (filling anomaly).

In those animals, compound A, on its own or in association with perindopril, makes possible a significant reduction in heart rate (Table 1 and Figure 1).

Table 1

			HF (untreated)	**HF + A**	**HF + perindopril**	**HF + A + perindopril**
Heart rate (bpm)	Duration of treatment	4 weeks	372.5	349.3	388.2	352.8
		12 weeks	387.2	342.7†	387.7	353.1†

† $p<0.05$ vs HF

Co-treatment with perindopril and compound A makes possible a significant increase in the shortening fraction of the left ventricle, that is to say an improvement in its contractility (Table 2 and Figure 2). Consequently, heart rate is improved compared to animals with heart failure that are not given treatment.

Table 2

	HF (untreated)	**HF + A**	**HF + perindopril**	**HF + A + perindopril**
shortening fraction (% of the diameter of the LV)	14.4	18.0	17.1	22.3†
heart rate (mL/min)	114	127	142†	140†

† $p<0.05$ vs HF

As Table 3 shows (Figure 3), the various systolic and diastolic parameters are modified by heart failure. The left ventricle contracts less well (dP/dt_{max} and LVESPVR significantly lower in the HF animals than in the healthy controls), which indicates systolic impairment. There is a major deterioration in diastolic function: the pressure inside the ventricle at the end of diastole is raised (LVEDP), the relaxation time (tau) is lengthened and the compliance (ability of the ventricle to distend) is low (LVEDPVR increased).

Table 3

	Control	HF (untreated)	HF + A	HF + perindopril	HF + A + perindopril
LVESP (mm Hg)	140	120	118	99	105
dP/dt_{max} (10^3mm Hg/s)	9.92	6.89*	6.78	5.97	7.69
LVESPVR (mm Hg/RVU)	26.4	11.1*	16.1†	16.4†	15.6†
LVEDP (mm Hg)	1.86	9.43*	4.89†	5.17†	3.32†
dP/dt_{min} (-10^3mm Hg/s)	10.24	5.66*	5.87	5.11	6.19
tau (ms)	3.54	12.64*	8.37†	7.31†	6.05†
LVEDPVR (mm Hg/RVU)	0.84	6.93*	2.70†	2.36†	1.37†‡

* $p<0.05$ vs control; † $p<0.05$ vs HF; ‡ $p<0.05$ vs HF+A and vs HF+perindopril

It is found that treatment of the animals which have heart failure, whether with perindopril on its own or with compound A on its own, improves systolic function, which can be seen from the LVESPVR, the only load-independent parameter.
The end diastolic pressure and relaxation time are clearly improved by perindopril on its own or by compound A on its own, and a tendency to a further reduction in those two parameters is noted when the two substances are administered together.
The compliance of the left ventricle (measured by LVEDPVR), the only load-independent parameter, is very clearly improved by perindopril and by compound A. Surprisingly, this effect is significantly increased when the animals are given the two treatments concomitantly.
In fact, the association of compound A and perindopril makes it possible to significantly improve the compliance, which returns to a level close to that of the control animals.
The association of perindopril and N-{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-N-methyl-3-oxo-1-propanamine accordingly makes it possible to improve the deterioration in diastolic function.

This effect on systolic function and diastolic function was then studied using the association of perindopril and a different I_f current inhibitor, ivabradine.
It is found that treatment with perindopril on its own or in association with ivabradine improves the systolic function (Table 4a and Figure 4a).
With respect to the diastolic dysfunction, treatment with perindopril and ivabradine is clearly more effective than perindopril on its own (the effect of ivabradine on its own is comparable to that of perindopril on its own, cf. Table 4b and Figure 4b).

The compliance of the left ventricle is returned to a level similar to that of the healthy animals.

Table 4a

	Control	HF (untreated)	HF + perindopril	HF + ivabradine + perindopril
LVESP (mm Hg)	163	134*	102†	100†
dP/dt$_{max}$ (10^3mm Hg/s)	10.11	7.68*	6.08†	6.10†
LVESPVR (mm Hg/RVU)	20.2	6.6*	14.5†	12.6†‡
LVEDP (mm Hg)	3.29	13.93*	6.88†	5.01†
dP/dt$_{min}$ (-10^3mm Hg/s)	10.63	5.54*	4.99	4.97
tau (ms)	3.21	14.29*	10.92†	8.52†
LVEDPVR (mm Hg/RVU)	0.79	4.06*	2.25†	1.15†‡

* $p<0.05$ vs control; † $p<0.05$ vs HF; ‡ $p<0.05$ vs HF+A and vs HF+perindopril

Table 4b

	Control	HF (untreated)	HF + ivabradine
LVESPVR (mm Hg/RVU)	35.53	9.66*	20.63*†
LVEDPVR (mm Hg/RVU)	0.85	5.33*	1.87*†

* $p<0.05$ vs control; † $p<0.05$ vs HF

These experiments show that, in a model of heart failure, the association of ivabradine or *N*-{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-3-(7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)-*N*-methyl-3-oxo-1-propanamine and perindopril makes possible an improvement in diastolic function which is greater than that obtained with one of those two treatments used on its own, this improvement allowing a return to normal diastolic function.

Pharmaceutical compositions:

Formula for the preparation of 1000 tablets each containing as active ingredients 7.5 mg of ivabradine and 2 mg of perindopril *tert*-butylamine:

Ivabradine hydrochloride.....8.085 g
Perindopril *tert*-butylamine.....2 g

Lactose monohydrate..... 62 g
Magnesium stearate ..... 1.3 g
Povidone ..... 9 g
Anhydrous colloidal silica..... 0.3 g
Cellulose sodium glycolate..... 30 g
Stearic acid ..... 2.6 g

Formula for the preparation of 1000 tablets each containing as active ingredients 10 mg of compound A and 2 mg of perindopril *tert*-butylamine:

Compound A fumarate .....12.48 g
Perindopril *tert*-butylamine..... 2 g
Lactose monohydrate..... 62 g
Magnesium stearate ..... 1.3 g
Povidone ..... 9 g
Anhydrous colloidal silica..... 0.3 g
Cellulose sodium glycolate..... 30 g
Stearic acid ..... 2.6 g

Other examples of pharmaceutical compositions according to the invention are given hereinbelow, without implying any limitation:

Example	**Ivabradine (mg)**	**Compound A (mg)**	**Perindopril *tert*-butylamine salt (mg)**	**Perindopril arginine salt (mg)**
1	10	-	2	-
2	15	-	4	-
3	10	-	-	2.5
4	15	-	-	5
5	-	60	2	-
6	-	80	4	-
7	-	60	-	2.5
8		80	-	5

Patentkrav

1. Assosiasjon av:

- ivabradine, eller 3-{3-[{[(7S)-3,4-dimetoksybicyklo[4.2.0]okta-1,3,5-trien-7-yl]-metyl}(metyl)amino]propyl}-7,8-dmetoksy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on eller én av dens addisjonssalter med en farmasøytisk akseptabel syre, deres hydrater og krystallinske former, eller
- N-{[(7S)-3,4-dimetoksybicyklo[4.2.0]okta-1,3,5-trien-7-yl]metyl}-3-(7,8-dimetoksy-1,2,4,5-tetrahydro-3H-benzazepin-3-yl)-N-metyl-3-okso-1-propanamin eller én av dens addisjonssalter med en farmasøytisk akseptabel syre, deres hydrater og krystallinske former,

med perindopril, eller én av dens addisjonssalter med en farmasøytisk akseptabel base, deres hydrater eller krystallinske former,
for anvendelse ved behandling av hjertesvikt med preservert systolisk funksjon.

2. Assosiasjon ifølge krav 1 for anvendelse i en behandlingsmetode ifølge krav 1, **karakterisert ved** at ivabradinen er i form av et hydroklorid eller ett av dets hydrater eller krystallinske former.

3. Assosiasjon ifølge krav 1 for anvendelse i en behandlingsmetode ifølge krav 1, **karakterisert ved** at N-{[(7S)-3,4-dimetoksybicyklo[4.2.0]okta-1,3,5-trien-7-yl]metyl}-3-(7,8-dimetoksy-1,2,4,5-tetrahydro-3H-benzazepin-3-yl)-N-metyl-3-okso-1-propanaminforbindelsen er i form av et hydroklorid eller fumarat eller én av deres hydrater eller krystallinske former.

4. Assosiasjon ifølge et av kravene 1 til 3 for anvendelse i en behandlingsmetode ifølge krav 1, **karakterisert ved** at peridopril-forbindelsen er i form av et tert-butylamin- eller arginin-salt eller én av deres hydrater eller krystallinske former.

5. Assosiasjon ifølge krav 1 for anvendelse i en behandlingsmetode ifølge krav 1, **karakterisert ved** at ivabradine-forbindelsen er i form av hydrokloridet eller ett av dets hydrater eller krystallinske former og perindopril-forbindelsen er i form av ter-butylamin- eller arginin-saltet eller ett av dets hydrater eller krystallinske former.

6. Assosiasjon ifølge krav 1 for anvendelse i en behandlingsmetode ifølge krav 1, **karakterisert ved** at N-{[(7S)-3,4-dimetoksybicyklo[4.2.0]okta-1,3,5-trien-7-

yl]metyl}-3-(7,8-dimetoksy-1,2,4,5-tetrahydro-3H-benzazepin-3-yl)-N-metyl-3-okso-1-propanaminet er i form av hydrokloridet eller fumaratet eller ett av deres hydrater eller krystallinske former og perindopril-forbindelsen er i form av tert-butylamin- eller arginin-saltet eller én av deres hydrater eller krystallinske former.

7. Farmasøytisk sammensetning omfattende, som aktive bestanddeler:

- ivabradine, i form av hydrokloridet eller én av dets hydrater eller krystallinske former, og
- perindopril, i form av tert-butylamin- eller arginin-saltet eller ett av dets hydrater eller krystallinske former,

alene eller i kombinasjon med én eller flere farmasøytisk akseptable eksipienter, for anvendelse ved behandling av hjertesvikt med preservert systolisk funksjon.

8. Farmasøytiske sammensetninger omfattende, som aktive bestanddeler:

- N-{[(7S)-3,4-dimetoksybicyklo[4.2.0]okta-1,3,5-trien-7-yl]metyl}-3-(7,8-dimetoksy-1,2,4,5-tetrahydro-3H-benzazepin-3-yl)-N-metyl-3-okso-1-propanamin, i form av hydrokloridet eller fumaratet eller ett av deres hydrater eller krystallinske former, og
- perindopril, i form av tert-butylamin- eller arginin-saltet eller ett av deres hydrater eller krystallinske former,

alene eller i kombinasjon med én eller flere farmasøytisk akseptable eksipienter, for anvendelse ved behandling av hjertesvikt med preservert systolisk funksjon.

Figure 1

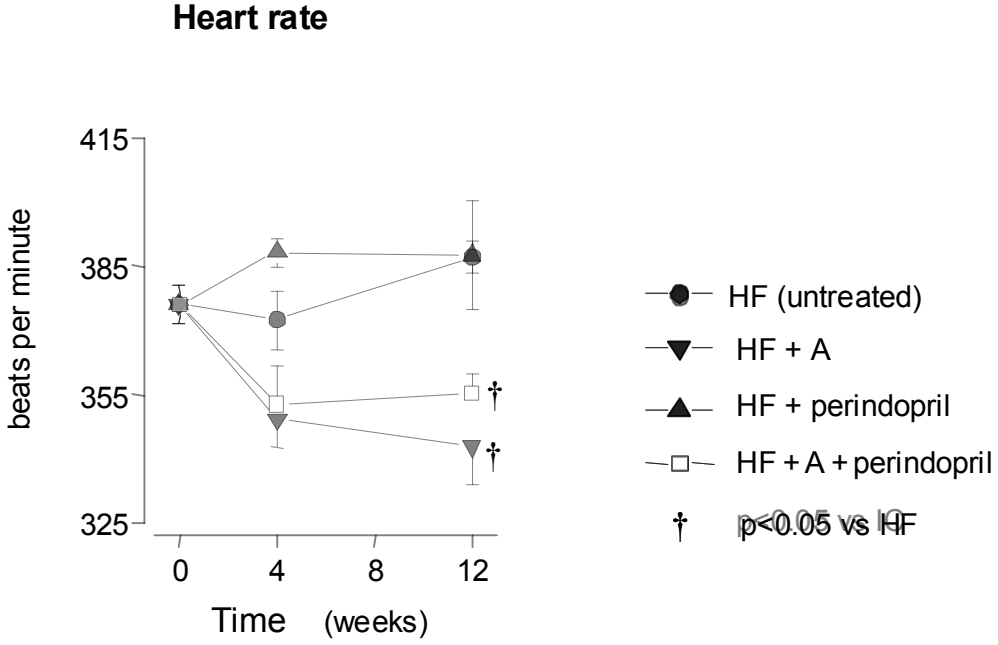

Heart rate
beats per minute
415
385
355
325
0
4
8
12
Time (weeks)
†
†
HF (untreated)
HF + A
HF + perindopril
HF + A + perindopril
† p<0.05 vs HF

Figure 2

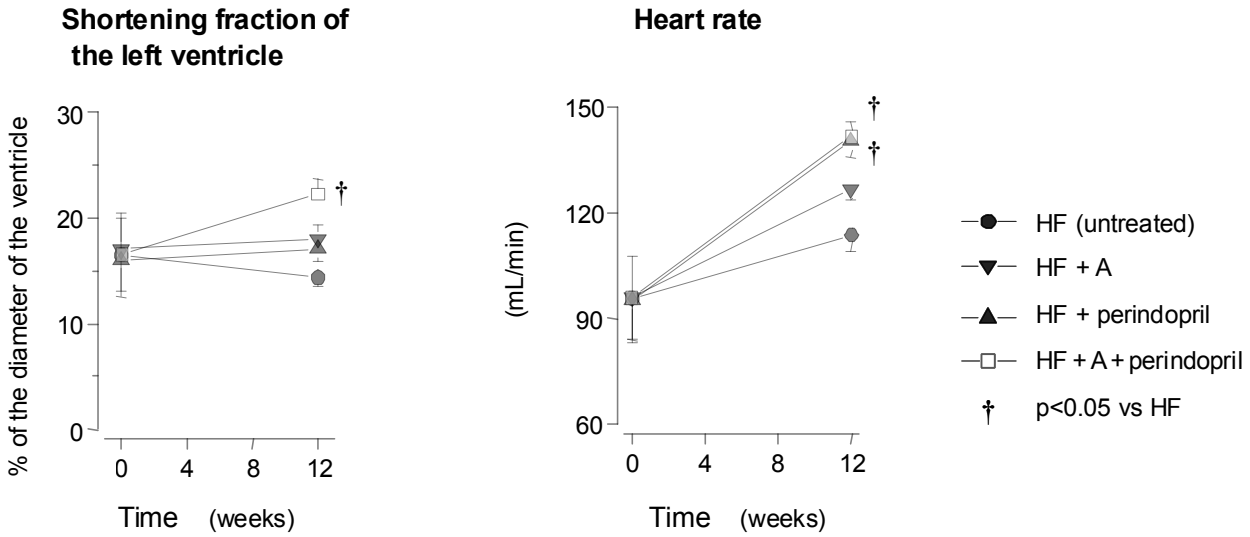

Shortening fraction of the left ventricle
% of the diameter of the ventricle
30
20
10
0
0
4
8
12
Time (weeks)
†
Heart rate
(mL/min)
150
120
90
60
0
4
8
12
Time (weeks)
†
†
HF (untreated)
HF + A
HF + perindopril
HF + A + perindopril
† p<0.05 vs HF

Figure 3

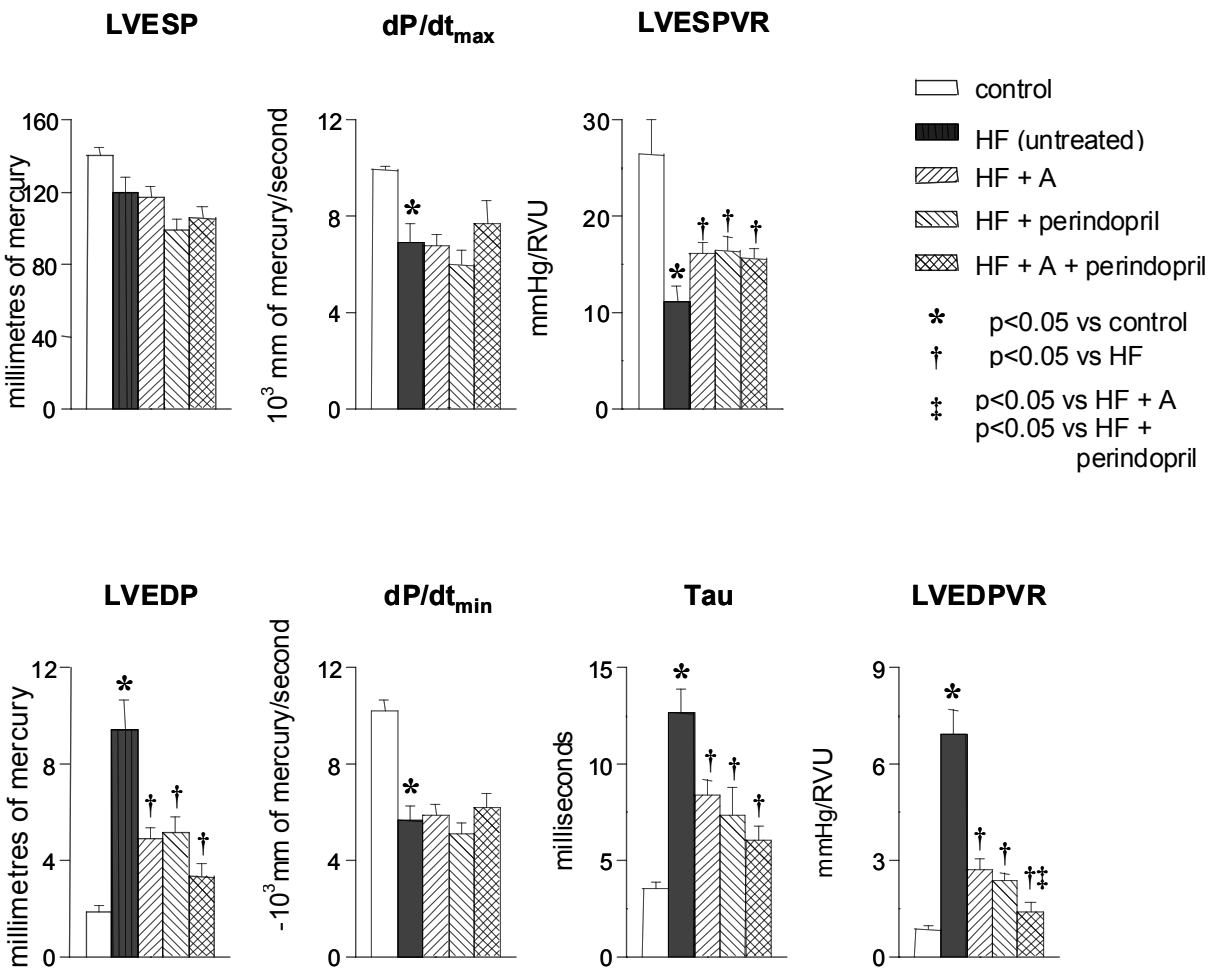

LVESP
millimetres of mercury
160
120
80
40
0
dP/dt$_{max}$
10^3 mm of mercury/second
12
8
4
0
LVESPVR
mmHg/RVU
30
20
10
0
control
HF (untreated)
HF + A
HF + perindopril
HF + A + perindopril
* p<0.05 vs control
† p<0.05 vs HF
‡ p<0.05 vs HF + A
p<0.05 vs HF + perindopril
LVEDP
millimetres of mercury
12
8
4
0
dP/dt$_{min}$
-10^3 mm of mercury/second
Tau
milliseconds
15
10
5
0
LVEDPVR
mmHg/RVU
9
6
3
0

Figure 4a

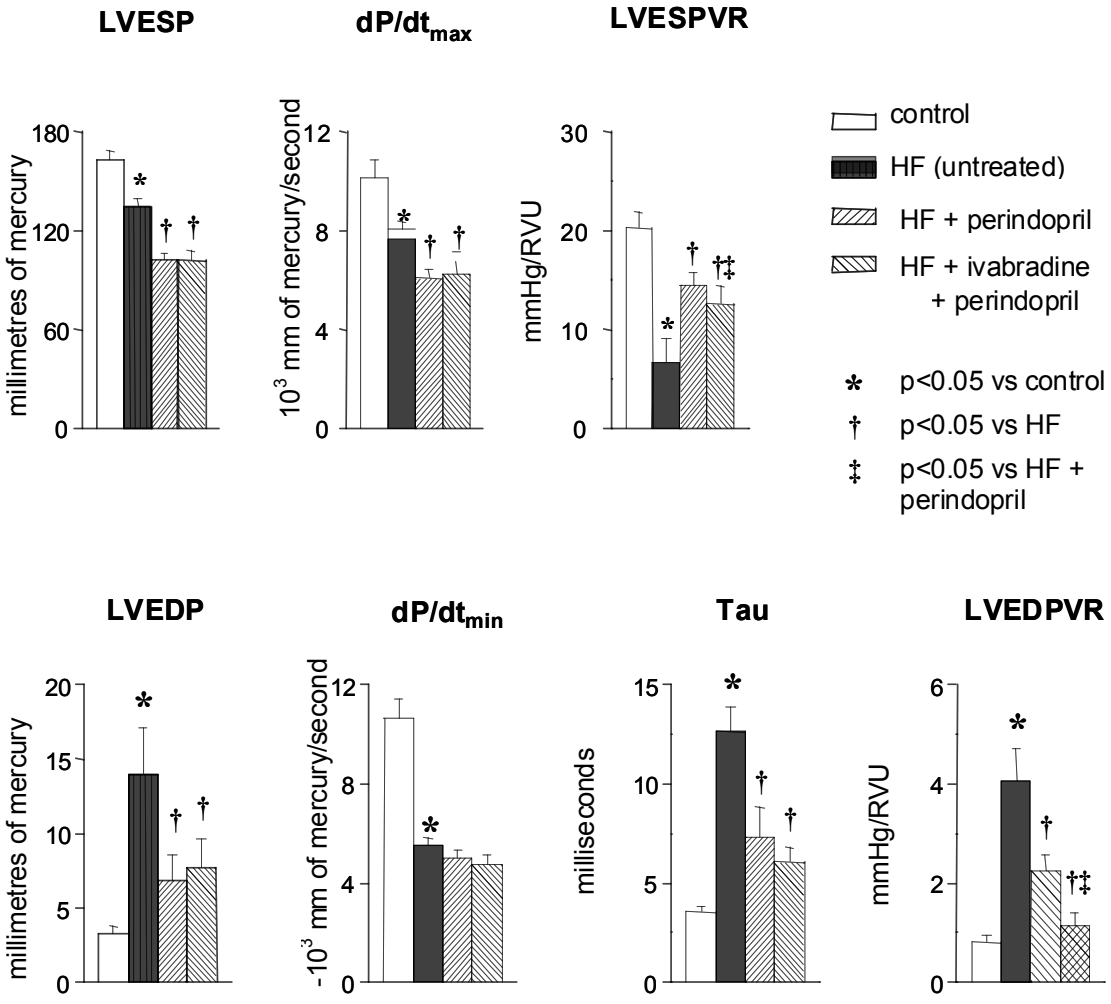
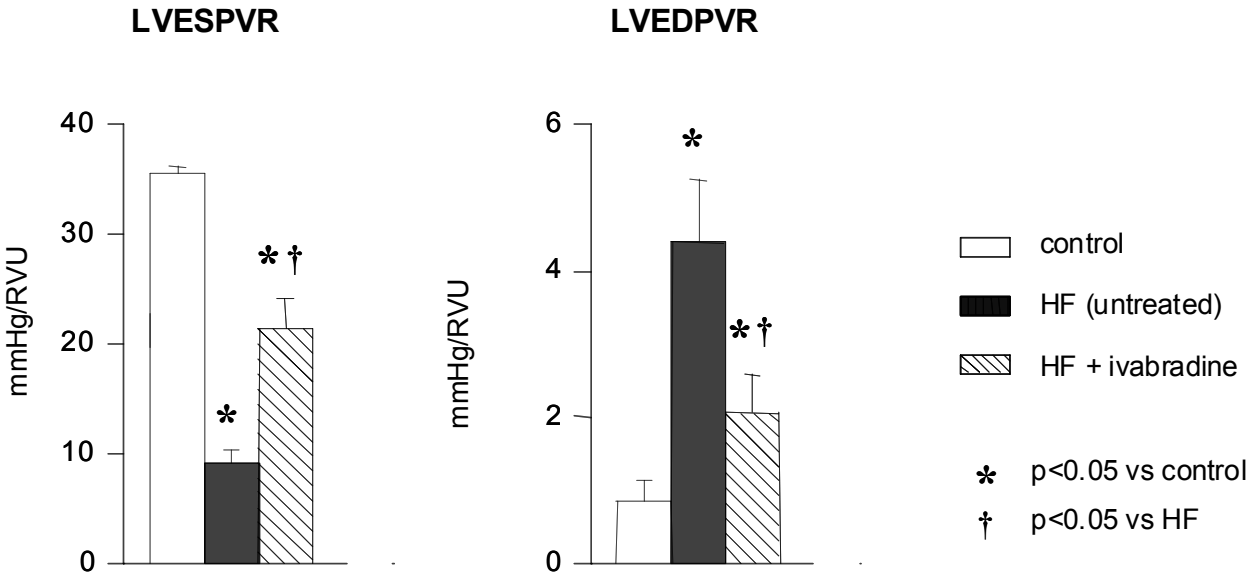

LVESP
dP/dt$_{max}$
LVESPVR
millimetres of mercury
180
120
60
0
10^3 mm of mercury/second
12
8
4
0
mmHg/RVU
30
20
10
0
control
HF (untreated)
HF + perindopril
HF + ivabradine + perindopril
* p<0.05 vs control
† p<0.05 vs HF
‡ p<0.05 vs HF + perindopril
LVEDP
dP/dt$_{min}$
Tau
LVEDPVR
millimetres of mercury
20
15
10
5
0
-10^3 mm of mercury/second
12
8
4
0
milliseconds
15
10
5
0
mmHg/RVU
6
4
2
0

Figure 4b


LVESPVR
LVEDPVR
mmHg/RVU
40
30
20
10
0
6
4
2
0
*
*†
control
HF (untreated)
HF + ivabradine
p<0.05 vs control
p<0.05 vs HF