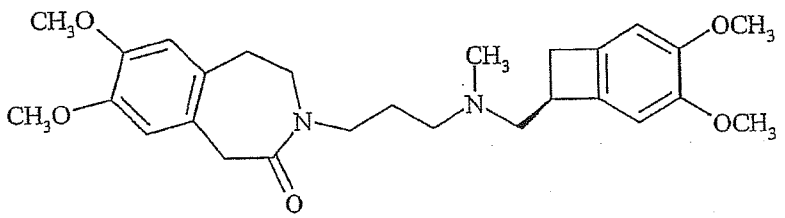
Association of a sinus node If current inhibitor and a beta blocker

The present invention relates to the fixed association of a sinus node If current inhibitor and a beta blocker, or β-blocker, and also to pharmaceutical compositions containing them.

More specifically, the present invention relates to a fixed association of a sinus node If current inhibitor which is 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-2H-3-benzazepin-2-one, of formula (I):



(I)

or one of its hydrates, crystalline forms or addition salts of any thereof with a pharmaceutically acceptable acid, and a β-blocker.

The present invention relates preferably to a fixed association between a β-blocker of the cardioselective type, more especially atenolol or one of its hydrates, crystalline forms or addition salts of any thereof with a pharmaceutically acceptable acid, and, as sinus node If current inhibitor, ivabradine hydrochloride or one of its hydrates or crystalline forms.

Sinus node If current inhibitors, more especially ivabradine and its hydrates and crystalline forms and addition salts thereof with a pharmaceutically acceptable acid, more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially negative chronotropic properties (lowering of heart rate), which make these

compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.

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

β-blockers, or β-blocking agents, are compounds which inhibit β-adrenergic receptors. β-blockers have the effect of slowing down the heart by decreasing the slope of depolarisation, reducing the heart's workload and reducing its oxygen demands. Consequently, β-blockers are used in the treatment of angina, especially in the prevention of attacks. In apparently paradoxical manner, β-blockers are used in the treatment of heart failure.

The β-blockers according to the invention are, preferably, cardioselective β-blockers, that is to say they preferentially block β1 cardiac receptors. Their cardioselective character makes it possible to reduce secondary effects, especially peripheral vasoconstriction and bronchoconstriction.
The cardioselective β-blockers are more especially selected from the following list: acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol and nebivolol.

The literature and the opinion leaders in the field of cardiovascular disorders generally conclude that it is difficult to demonstrate the superiority of associations comprising a β-blocker plus another class of anti-angina compounds over β-blocker monotherapy in the treatment of stable angina.

The present invention demonstrates, surprisingly, that sinus node If current inhibitors and, more especially, ivabradine are capable of potentiating the effects of β-blockers on increasing exercise capacity. Accordingly, this increasing of exercise capacity is related to a synergy between the active ingredients, i.e. a sinus node If current inhibitor and a β-blocker.

In the pharmaceutical compositions according to the invention, the amounts of sinus node If current inhibitor and of β-blocker are matched to the nature of those active ingredients and their relative proportions are accordingly variable as a function of said active ingredients.

The pharmaceutical compositions according to the invention have proportions of from 1.6 % to 80 % of the total weight of the active ingredients for the sinus node If current inhibitor and from 20 % to 98 % of the total weight of the active ingredients for the β-blocker.

When the sinus node If current inhibitor is ivabradine in hydrochloride salt form and the β-blocker is atenolol, the preferred percentages for that association are around 25 % ivabradine in hydrochloride salt form as opposed to 75 % atenolol.

The present invention relates also to pharmaceutical compositions comprising, as active ingredient, an association of a sinus node If current inhibitor and a β-blocker, optionally in the form of pharmaceutically acceptable salts, on their own or together with one or more appropriate, inert, non-toxic carriers or excipients.

In the pharmaceutical compositions according to the invention, the weight proportion of active ingredients (weight of active ingredients over total weight of the composition) is advantageously from 5 to 50 %.

As regards the pharmaceutically acceptable excipients, there may be mentioned, without implying any limitation, binders, diluents, disintegrating agents, stabilisers, preservatives, lubricants, fragrances, aromas or sweeteners.

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: aluminium and magnesium silicate, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone.

Among the pharmaceutical compositions according to the invention, there will be more especially selected those that are suitable for administration by the oral, parenteral and especially intravenous, per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory routes, more specifically tablets or dragées, sublingual tablets, hard gelatin capsules, glossettes, capsules, lozenges, injectable preparations, aerosols, eye drops, nose drops, suppositories, creams, ointments or dermal gels.

The preferred route of administration is the oral route and the corresponding pharmaceutical compositions may allow instantaneous or deferred release of the active ingredients.

Preferred pharmaceutical compositions are tablets.

The dosage can be varied according to the nature and severity of the disorder, the administration route and also the age and weight of the patient. In the compositions according to the invention it ranges from 25 to

150 mg for the β-blocker and from 2.5 to 30 mg of sinus node If current inhibitor per 24 hours in one or more administrations. Preferably, when the sinus node If current inhibitor is ivabradine, the administration dose is from 5 to 7.5 mg twice per day (b.i.d.). When the β-blocker is atenolol, the daily administration dose is preferably 50 mg in one administration.

Finally, the pharmaceutical compositions according to the invention are useful in the manufacture of medicaments intended for the treatment of angina pectoris, ischaemia and heart failure.

The examples of compositions hereinbelow are given by way of non-limiting example.

Ivabradine / atenolol tablets:

Example 1 :

Constituents	Amount (mg)
ivabradine hydrochloride	5
atenolol	50
hydrophobic colloidal silica	0.4
starch	6
magnesium stearate	2
microcrystalline cellulose	50
lactose	86.6
For a tablet totalling	200

Example 2 :

Constituents	Amount(mg)
ivabradine hydrochloride	7.5
atenolol	50
hydrophobic colloidal silica	0.4
starch	6
magnesium stearate	2
microcrystalline cellulose	50
lactose	84.1
For a tablet totalling	200

Clinical study:

The patients selected for this clinical study are men and women from 18 to 75 years of age who have suffered from angina pectoris for at least 3 months and been treated with β-blockers such as atenolol (50 mg o.d.) or any other β-blocker at an equivalent dose for at least 3 months. These patients have, despite their treatment, a positive exercise tolerance test (ETT) and daily symptoms of angina pectoris.

This double-blind, parallel-group, international clinical study was carried out in 889 patients. The patients, all of whom are receiving atenolol, are randomised into two groups:

- in addition to the β-blocker, the first group is given ivabradine (hydrochloride) at a dose of 5 mg twice a day for two months and then at a dose of 7.5 mg twice a day for a further two months;
- in addition to the β-blocker, the second group is given a placebo for 4 months.

The patients are subjected to a treadmill exercise tolerance test (ETT) in accordance with the Bruce protocol before ivabradine is administered (that is when receiving β-blocker on its own), and after 4 months of treatment with the association between ivabradine and atenolol. The principal parameters measured in the course of the effort test are:

- total exercise duration (TED) - the TED includes the time taken for the treadmill to come to a stop or, that is, a duration of about 10 seconds starting from the patient's request to stop the exercise;
- the time until the "angina pectoris" pain forces the patient to stop the exercise (TLA);
- the time until the onset of the "angina pectoris" pain (TAO);
- the time taken for a 1 mm ST segment depression (TST) to appear on the electrocardiographic recording, this being a reflection of ischaemia and corresponding to the electrical sign of pain in the cardiac muscle.

These measurements are made at trough activity of the association of active ingredients or, that is, 12±1 hours and 24±2 hours after administration of the active ingredients.

The ivabradine/β-blocker association according to the invention ensures good acceptability and good safety of use according to the data from the compliance summary.

The patients have a mean age of 60±8 years. On entry into the study, the mean systolic/diastolic arterial pressure and heart rate of the patients at rest are respectively, on average: 127±12 / 78±7 mmHg and 67±7 beats per minute. After 4 months of treatment with the association, the heart rate has reduced by 9±10bpm (β-blocker + placebo 1±10bpm).

The mean improvements in the various parameters measured during the treadmill exercise test, between the value measured before the start of

treatment with ivabradine and the end of the treatment period, are set out in the table below:

	β-blocker + ivabradine (n=441)	β-blocker + placebo (n=434)	p-value
TED	24±65	8±64	p< 0.001
TAO	49±83	23±79	p< 0.001
TLA	26±66	9±64	p< 0.001
TST	46±93	15±87	p< 0.001

Improvements in parameters (in seconds, mean ± SD)

This study shows that ivabradine is capable of improving exercise tolerance in patients already receiving a standard dose of β-blockers.

The high level of compliance (99 % in the patients receiving ivabradine) and the low percentage of serious adverse events show the acceptability and safety of the association of ivabradine plus β-blocker compared to the β-blocker in monotherapy.

CLAIMS

1. Association of a sinus node If current inhibitor which is ivabradine and a β-blocker which is atenolol or bisoprolol.

2. Association of a sinus node If current inhibitor which is 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 one of its hydrates, crystalline forms or addition salts of any thereof with a pharmaceutically acceptable acid and a β-blocker which is atenolol or one of its hydrates, crystalline forms or addition salts of any thereof with a pharmaceutically acceptable acid or bisoprolol or one of its hydrates, crystalline forms or addition salts of any thereof with a pharmaceutically acceptable acid.

3. Association according to either claim 1 or claim 2, characterised in that the sinus node If current inhibitor is 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 - hydrochloride or one of its hydrates or crystalline forms.

4. Pharmaceutical composition comprising, as active ingredient, an association according to one of claims 1 to 3, on its own or in combination with one or more pharmaceutically acceptable excipients.

5. Pharmaceutical composition according to claim 4 for use in the manufacture of a medicament for the treatment of angina pectoris, ischaemia and heart failure.

6. Use of an association according to one of claims 1 to 3 in the manufacture of a medicament for the treatment of angina pectoris, ischaemia and heart failure.

7. Use of a pharmaceutical composition according to one of claims 4 to 5 in the manufacture of a medicament for the treatment of angina pectoris, ischaemia and heart failure.