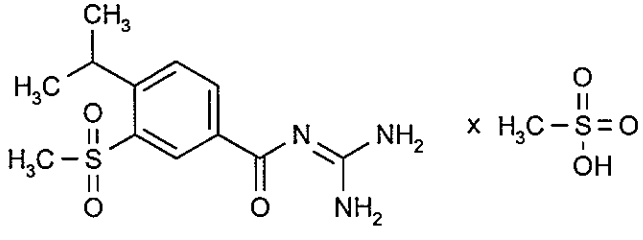
Description

Combination product of the sodium-hydrogen exchange inhibitor cariporide with ACE inhibitors for preventing heart failure and other age-related organ dysfunctions, age-related disorders and for prolonging life

The invention describes a combination of cariporide (Hoe 642), an inhibitor of the cellular sodium-hydrogen exchanger, the ACE inhibitor ramipril, and to the use thereof in human and veterinary medicine for preventing heart failure and other age-related functional disturbances and dysfunctional changes in organs of the body and for preventing age-related disorders and for prolonging life while preserving an improved quality of life.

WO 00/38661 describes the use of inhibitors of the sodium-hydrogen exchanger (NHE) for producing a medicament for preventing age-related organ dysfunction, age-related disorders and for prolonging life. In this case, inhibitors of the cellular sodium-hydrogen exchanger are described for the production of a medicament for preventing age-related functional disturbances and dysfunctional changes in organs of the body and for preventing age-related disorders and for prolonging life while preserving an improved quality of life. Typical representatives of NHE inhibitors which are mentioned are cariporides and their pharmaceutically acceptable salts, e.g. cariporide mesilate having the following formula:

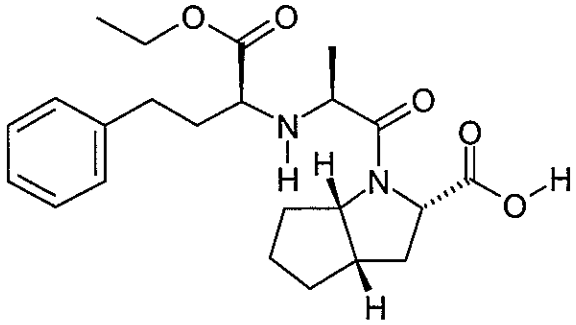


In the text which follows, the free base of cariporide and its pharmaceutically acceptable salts, including cariporide mesilate, are included in the term cariporide.

WO 00/38661 recorded the biological findings on normotensive healthy rats.

Angiotensin converting enzyme (ACE) inhibitors, for example ramipril, have, in contrast to NHE inhibitors, no protective effect at all on the described pathological age-related organ changes in old normotensive rats. Furthermore, WO 00/38661 considers combination of NHE inhibitors with medicaments which lower blood pressure, such as with ACE inhibitors, angiotensin receptor antagonists etc., in order to utilize, in addition to the protective effect of NHE inhibitors against ageing, the possible benefit of a lowering effect on blood pressure by hypotensive agents. An increase in a life-prolonging effect or a protective effect on pathological age-related organ changes was not expected.

It has been known for some time from the literature that ramipril, having the formula



significantly prolongs the life span of spontaneously hypertensive rats which is shortened as a consequence of their hypertensive disorder.

It is now shown in the present experimental findings that NHE inhibitors, on their own and in combination with ACE inhibitors, likewise cause a significant life-prolonging effect and a protective effect on pathological age-related organ changes in spontaneously hypertensive rats (SHR). In order to exclude a blood pressure-lowering effect by the ACE inhibitor ramipril as secondary effect for a possible prolonging of life, ramipril was used in a subthreshold dose in relation to lowering blood pressure. There were moreover, in a surprising way, significantly more favorable age-protective effects on combination treatment with the NHE inhibitor cariporide and the ACE inhibitor ramipril while there was no lowering effect on blood pressure. The combination treatment is significantly superior to the two individual products.

A subthreshold dose, not lowering the blood pressure, of ramipril in rats is normally in

a range from 1 to 50 μg per kg of body weight and per day. In humans, a subthreshold dose of ramipril on administration to a person with a body weight of about 70 kg is generally in a range from 0.1 to 1.0 mg per day and person, preferably 0.3 to 0.7 mg per day and person, for example 0.625 mg per day and person.

For the experiments, old spontaneously hypertensive rats (age = 18 months) were treated either with the NHE inhibitor cariporide, or with a subthreshold dose, which did not lower the blood pressure, of the ACE inhibitor ramipril or with a corresponding combination of the two active ingredients. This hypertensive rat model is generally regarded as representative for human essential hypertension. 27 hypertensive rats 18 months old were employed for each experimental group. 3 months after the start of treatment, when the number of surviving animals in the placebo control group was only 7, an interim analysis was carried out on 7 animals from each group. The hearts of the SHRs treated with low ramipril doses showed a significant reduction in the force of mycocardial contraction compared with the placebo control hearts. In contrast to this, cariporide and the ramipril/cariporide combination significantly improved the function of the heart.

Likewise, the myocardial fibrosis, which correlates with heart failure, was significantly reduced by cariporide monotherapy and by the ramipril/cariporide combination. The significantly smaller weights of the hearts likewise show the antifibrotic effect, which is directed against the development of heart failure, of the ramipril/cariporide combination and of cariporide.

The individual products ramipril and cariporide lead to an improvement in the survival rate compared with the placebo treatment. No significant differences in the survival rates with cariporide and ramipril were detectable in this case. Suprisingly, the cariporide/ramipril combination leads to a significant increase in the survival rate compared with the effects produced by the individual compounds.

Cariporide can thus be used according to the invention together with ramipril in an advantageous manner as pharmaceutical in animals, preferably in mammals, and

especially in humans. The invention relates to the combination of cariporide and ramipril for use in human medicine and veterinary medicine, for example in dogs. The two active ingredients can be combined in such a way that cariporide and ramipril are administered together in one medicament (combination product) or that a medicament which comprises one active ingredient cariporide and a separate medicament which comprises ramipril are administered concurrently or successively in any sequence. Administration successively includes a combination in which the individual medicaments are administered at different times and by different routes in order to achieve a better effect. However, it may also be expedient firstly to administer a suitable dose of one medicament and subsequently to administer the other medicament, e.g. by infusion, until the desired combination effect, e.g. improved heart function, has occurred. Depending on the circumstances of the individual case, it may be more beneficial to administer cariporide and ramipril in the form of a pharmaceutical combination product in which the two active ingredients are present in a fixed ratio of amounts, or to administer them in the form of separate individual pharmaceutical products. In the latter case, in which the ratio of amounts of the two active ingredients can be varied, it is possible for the individual products to be present in suitable primary packaging and, where appropriate, together with instructions for use, referring to the use according to the invention, in a joint package, or for the individual products where appropriate to be present, each together with the instructions for use, referring to the use according to the invention, in separate packages. All such products and presentations are encompassed by the present invention.

The ratio by weight of cariporide to ramipril in the combinations of the invention is normally in a range from 1:0.0001 to 1:1, preferably between 1:0.0001 and 1:0.1, for example between 1:0.0005 and 1:0.01

The present invention further relates to pharmaceutical preparations which comprise as active ingredient both cariporide and ramipril in addition to conventional pharmaceutically acceptable carriers and excipients. The pharmaceutical preparations normally comprise 0.01 to 90 percent by weight of cariporide and ramipril. The pharmaceutical preparations can be produced in a manner known per se. For this

purpose, the active ingredients are converted together with one or more solid or liquid pharmaceutical carriers and/or excipients into a suitable administration form or dosage form which can then be used as pharmaceutical in human medicine or veterinary medicine. Corresponding statements apply to pharmaceutical preparations comprising the active ingredients cariporide and ramipril separately and employed according to the invention.

Particularly claimed are cariporide and ramipril combination products for inhibiting the development of age-related disorders in human or veterinary medicine, for inhibiting the development of age-related organ damage, for prolonging life and/or for preventing or inhibiting further progression of heart failure and partial regression of the disorder.

The present invention also relates to the use of cariporide and ramipril for producing a pharmaceutical preparation and to the use thereof as medicament for inhibiting the development of age-related disorders in human or veterinary medicine, for inhibiting the development of age-related organ damage, for prolonging life and/or for preventing or inhibiting further progression of heart failure and partial regression of the disorder.

The dosage of the active ingredients cariporide and/or ramipril to be administered depends on the individual case and should be adapted to the circumstances of the individual case as usual for an optimal effect. Thus, it depends of course on the frequency of administration and on the nature of the pharmaceutical formulations employed in each case for therapy or prophylaxis, but also on the nature and severity of the disease to be treated, and on the sex, age, weight and individual response of the person or animal to be treated and on whether the therapy is acute or chronic or the aim is prophylaxis. On use of the inventions as pharmaceuticals in animals, preferably in mammals, and especially in humans, the dosage of ramipril may vary in the range from 0.1 to 10 mg per day and per person (with a body weight of about 70 kg), preferably from 0.1 to 5 mg per day and person, particularly preferably from 0.2 to 2.5 mg per day and person. The ramipril dose may also be given in a subthreshold range from 0.1 to 1 mg per day and person, preferably from 0.3 to 0.7 mg per day and person. The dose of cariporide may vary between 50 mg and 1 g per day and person,

preferably between 100 to 500 mg per day and person. It is possible for example for the ramipril dose to be 0.625 mg per day and person and for the cariporide dose to be 200 mg per day and person.

With the combination treatments of the invention it is possible for cariporide and ramipril to be administered in lower doses than on administration of only one of the two active ingredients.

With the combination treatment of the invention it is possible for the daily dose of the active ingredients to be administered all at once or for it to be divided into a plurality of, for example, two, three or four, administrations.

Pharmaceuticals which comprise cariporide and ramipril combinations of the invention can be administered orally, parenterally, e.g. intravenously, rectally, transdermally or topically, the preferred administration being dependent on the individual case.

The excipients suitable for the desired pharmaceutical formulation are familiar to the skilled worker on the basis of his expert knowledge. Besides solvents, gel formers, suppository bases, tablet excipients and other active ingredient carriers, it is possible to use for example antioxidants, dispersants, emulsifiers, antifoams, masking flavors, preservatives, solubilizers, agents for achieving a depot effect, buffer substances or colors.

For a form for oral use, the active compounds are mixed with the additives suitable for this purpose, such as carriers, stabilizers or inert diluents, and converted by conventional methods into the suitable administration forms such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily solutions. Examples of inert carriers which can be used are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, especially corn starch. Preparation is preferable both as dry and as wet granules. Examples of suitable oily carriers or solvents are vegetable or animal oils such as sunflower oil or fish liver oil. Examples of suitable solvents for aqueous or alcoholic solutions are water, ethanol or sugar

solutions or mixtures thereof. Examples of further excipients, also for other administration forms, are polyethylene glycols and polypropylene glycols.

For subcutaneous or intravenous administration, the active compounds are converted, if desired with the substances usual for this purpose, such as solubilizers, emulsifiers or further excipients, into a solution, suspension or emulsion. Examples of suitable solvents are water, physiological saline or alcohols, e.g. ethanol, propanol, glycerol, as well as sugar solutions such as glucose or mannitol solutions, or else mixtures of the various solvents mentioned.

Experimental data

The effect of a combination of ramipril and cariporide on the survival rate, fibrosis and the heart weights of rats with genetically related hypertension was investigated.

For this purpose, old spontaneously hypertensive rats (age = 18 months) were treated either with the NHE inhibitor cariporide, or with a subthreshold dose, which did not lower the blood pressure, of the ACE inhibitor ramipril or with a corresponding combination of the two active ingredients. 27 hypertensive rats 18 months old were employed for each of the four treatment methods. 400 mg/kg of body weight of cariporide were administered via the feed (0.6% cariporide in standard rat diet) and 10 μg/kg of body weight of ramipril were administered via the drinking water as daily dose. Three months after the start of treatment, when only n = 7 surviving animals remained in the placebo control group, an interim analysis was carried out with n = 7 animals from each group. The treatment methods indicated above were applied continuously from the 18th month for the remaining rats still surviving in each group. To demonstrate that the ramipril dose did not lower the blood pressure, regular measurements of the rats' blood pressure were carried out by the tail cuff method, with no significant differences being detectable in the four treatment groups.

Thus, 20 rats 18 months of age were employed for investigating the survival rate for each experiment group (Table 1). The results of observation are compiled in Table 2.

Group	Treatment	N
1	Placebo	20
2	Ramipril	20
3	Cariporide	20
4	Combination	20

Tab. 1: Experimental groups

Age (month)	Placebo	Cariporide	Ramipril	Combination
18	20	20	20	20
19	10	18	18	20
20	4	16	15	18
21	0	12	11	18
22	0	8	9	18
23	0	7	4	16
24	0	7	0	14
25	0	5	0	13
26	0	0	0	8
27	0	0	0	7
28	0	0	0	3
29	0	0	0	0

Tab. 2: Number of surviving rats

An investigation of whether an improvement in the survival rate compared with placebo is detectable for the product groups, and whether an improvement in the survival rate

compared with the individual products is detectable for the combination follows.

Descriptive analysis

Figure 1 shows the profile of the survival rate for all treatment groups in detail. There are evidently distinct differences between placebo and product groups on the one hand and between the individual products and the combination after the experiment had lasted only 3-4 months.

The combination treatment provided the best results throughout the experimental period. It is likewise evident that the placebo control was distinctly inferior to all the treatments.

Statistical analysis

Table 3 shows the results of all pairwise comparisons of respectively two treatment groups. The test results apply at a multiple significance level of 5%.

Group	vs. Group	Test
Placebo	Cariporide	*
	Ramipril	*
	Combination	*
Combination	Ramipril	*
	Cariporide	*
Ramipril	Cariporide	n.s.

Tab. 3: Holm-adjusted log rank tests.

* indicates significant difference, n.s. = not significant

All the product groups are statistically significantly different from the placebo group, which can be interpreted together with figure 1 as efficacy of the treatments. Figure 1 additionally reveals distinct advantages of the combination compared with the individual products.

Median survival time

Table 4 shows estimates of the median dropout time, the time at which the survival rate in the population of experimental animals just reaches 50%.

Group	Median	95% interval
Placebo	1.5	[1, 2)
Cariporide	4.0	[3, 7)
Ramipril	4.0	[3, 5)
Combination	8.0	[6, 10)

Tab. 4: Median survival time

According to this, the proportion of surviving animals in the placebo group has fallen to 50% after only 1.5 months, whereas this is not to be expected until after 8 months with a combination treatment.

The individual products achieve a median survival time of 4 months which is less than

half that of the combination product.

Statistical methods

The statistical analysis was carried out essentially using the SAS/STAT procedure LIFETEST [SAS Institute Inc (1989): SAS/STAT User's Guide, Version 6, 4th Edition, Volume 2; Cary, NC; SAS Institute Inc.]. The log rank tests were carried out pairwise on respectively two experimental groups and adjusted to obtain a multiple significance level of 5% according to S. Holm (1979): A Simple Sequentially Rejective Multiple Test Procedure; Scand. J. Statist.; 6, pp. 65-70.

Conclusion on the survival rates

The individual products ramipril and cariporide lead to a statistically significant improvement in the survival rate compared with the placebo treatment. No significant differences in the survival rates with cariporide and ramipril were detectable at the chosen significance level. The combination treatment is significantly superior to the two individual products.

The chronic hypertension leads in the old spontaneously hypertensive animals to transformation processes in myocardial tissue which essentially correspond to those taking place in humans (In an early phase (months 10–15 of life) compensated heart failure with hypertrophy (NYHA stage I-II) and in the later phase (months16–21 of life) decompensated heart failure with ventricular dilatation and fibrosis (NYHA stage III-IV)).

As mentioned above, an interim analysis with n = 7 animals from each group was carried out 3 months after the start of treatment, when only n = 7 surviving animals remained in the placebo control group. Determinations were carried out inter alia of the total heart weight and the weights of the left and right ventricle and the molar ratio of hydroxyproline to ariginine in the heart tissue (determined by HPLC), which is a marker

of myocardial fibrosis. Interestingly, it was possible for a preexisting fibrosis to be reduced by late-onset treatment with cariporide, but not with ramipril and an even greater reduction in fibrosis was observed with the ramipril/cariporide combination (Fig. 2). These effects are also reflected in the weights of the hearts (Fig. 3).

The captions and titles used in the drawings are as follows:

Fig. 1: Kaplan-Meier survival times

Y axis: survival rate (1 = 100%)

X axis: time in months from the start of treatment (start of treatment = 0, identical to the 18th month of life)

Fig. 2: Effect of late treatment with cariporide and ramipril on myocardial fibrosis in old spontaneously hypertensive rats

Y axis: product groups

X axis: hyp/arg is the ratio of hydroxyproline to arginine and is regarded as a fibrosis marker

* means $p < 0.05$ vs placebo

n = 7 per group

Fig. 3: Effect of late treatment with cariporide and ramipril on the weight of the hearts of spontaneously hypertensive rats

Y axis: product groups

X axis: mg heart weight per 100 g body weight

 Complete heart

 Left ventricle

 Right ventricle

* $p < 0.05$ vs placebo

n = 7 per group

Summary of the results

The present results show that therapy with a combination of the NHE1 inhibitor cariporide and ramipril has a life-prolonging effect and inhibits the progression of or partially reverses age-related organ damage, in particular heart failure even with late-onset therapy and/or hypertensive diseases.

Patent claims:

1. A cariporide and ramipril combination product.

2. A cariporide and ramipril combination product as claimed in claim 1 for inhibiting the development of age-related disorders in human and veterinary medicine.

3. A cariporide and ramipril combination product as claimed in one and more of claims 1 and 2 for inhibiting the development of age-related organ damage in human or veterinary medicine.

4. A cariporide and ramipril combination product as claimed in one and more of claims 1, 2 and 3 for prolonging life in human or veterinary medicine.

5. A cariporide and ramipril combination product as claimed in one and more of claims 1, 2 and 3 for preventing or inhibiting further progression of heart failure and for partial regression of the disorder in human or veterinary medicine.

6. The use of cariporide in combination with ramipril for producing a medicament for inhibiting the development of age-related disorders in human or veterinary medicine.

7. The use of cariporide in combination with ramipril as claimed in claim 6 for producing a medicament for inhibiting the development of age-related organ damage in human or veterinary medicine.

8. The use of cariporide in combination with ramipril as claimed in claims 6 and/or 7 for producing a medicament for prolonging life in human or veterinary medicine.

9. The use of cariporide in combination with ramipril as claimed in claims 6 and/or 7 for producing a medicament for preventing or inhibiting further progression of heart failure and for partial regression of the disorder in human or veterinary medicine.

10. A product comprising cariporide in combination with ramipril for concurrent, separate or sequential use for inhibiting the development of age-related disorders, for inhibiting the development of age-related organ damage, for prolonging life and/or for preventing or inhibiting further progression of heart failure and for partial regression of the disorder in human or veterinary medicine.