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The invention relates to favourable combinations of the thiazide diuretic chlorthalidone with Angiotensin II Receptor Blockers (ARBs) for the treatment of hypertension.

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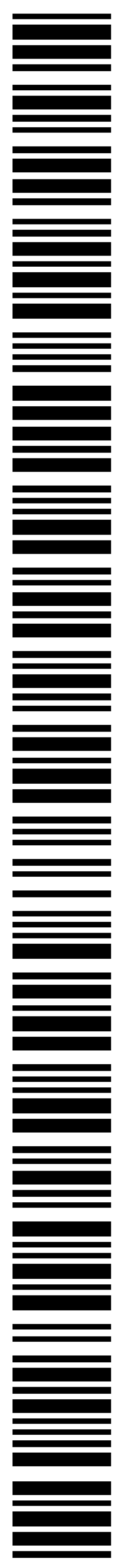
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CHLORTHALIDONE COMBINATIONS

The present invention relates to the thiazide diuretic Chlorthalidone and particularly addresses its use in combination with Angiotensin II Receptor Blockers (ARBs).

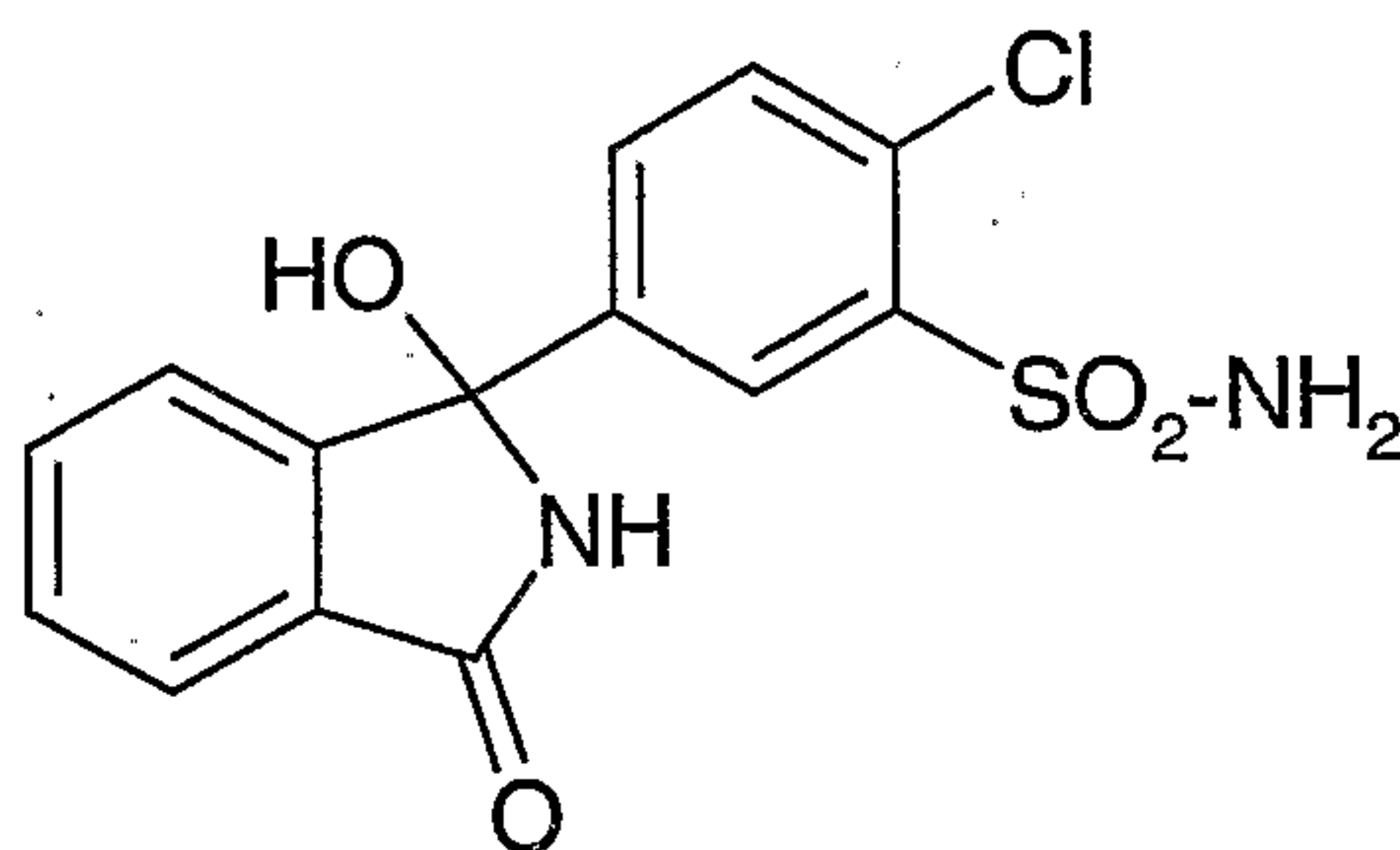
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Thiazide diuretics cause the kidneys to increase the amount of salt and water eliminated from the body in the urine. They are classified by their chemistry and their specific pharmacological effect on the kidney. Originally used to treat patients with edema they were found to reduce blood pressure and became the first-line drug in antihypertensive therapy.

10

Chlorthalidone is usually grouped with the thiazides because it has the same pharmacological effect on the kidney even though it is chemically different. It's CAS name is 2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)benzene-sulfonamide having the following structure:

15



The precise mechanism by which thiazides reduce blood pressure is unknown. The addition of thiazide diuretics to ARB therapy has been shown to improve the ability of ARBs to lower BP.

20

While angiotensin II converting enzyme (ACE) inhibitors interfere with the generation of angiotensin II, ARBs lower blood pressure (BP) by specifically blocking angiotensin II activity at angiotensin II subtype 1 receptor sites independent of the pathway of angiotensin II generation. Adverse effects of ACE inhibitors which appear unrelated to angiotensin II blockade like cough and angioedema can be avoided with ARBs. They have been shown to provide cardiovascular and renal protection, independent of their effects on systemic BP. As is the case with other antihypertensive drugs, monotherapy with ARBs does not always

25

reduce BP to recommended levels in hypertensive individuals, and ARBs show a limited dose-responsiveness, i.e. their BP-lowering effect often cannot be significantly improved by simply increasing the dose.

5 When combining ARBs with thiazide diuretics in hypertension therapy available thiazides such as bendrofluazide, bendroflumethiazide, benzthiazide, chlorothiazide, cyclopenthiazide, hydrochlorothiazide (HCTZ), hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, quinethazone, trichlormethiazide or xipamide are generally considered equally effective. It is the merit of the present invention to identify chlorthalidone
10 as a preferred thiazide diuretic for combination therapy if reduction of systolic BP is a major concern. Thus, by combining the sodium salt of the ARB telmisartan with chlorthalidone instead of hydrochlorothiazide, at least an additional 2-4 mmHg up to 10 mmHg reduction in systolic BP can be achieved. This appears particularly favourable when treating elderly
15 people, since the prevalence of systolic hypertension increases with age. Additionally, the longer duration of the antihypertensive effect of chlorthalidone (mean plasma half-life of 40-60 hours) compared to hydrochlorothiazide (mean plasma half-life of about 24 hours) can be favourably combined with the action profile of the various ARBs to achieve an efficient 24-hour blood pressure control, which allows once-daily dosing without compromising BP control at the end of the dosing period.

20 Thus, it is an objective of the present invention to provide a pharmaceutical preparation or fixed dose combination comprising as active ingredient chlorthalidone and an angiotensin II receptor blocker (ARB) including pharmaceutically acceptable salts thereof. Usually the combination consists of the two active ingredients in admixture with one or more excipients
25 (adjuvants). Particularly preferred preparations are those for oral administration such as tablets, sugar-coated tablets, capsules, powders, suspensions or suppositories. Preferred embodiments of tablets may comprise two or more layers.

A comprehensive list of ARBs can be found on pages 7-18 of WO 95/26188. Particularly
30 suitable ARBs are described in EP-A-253310, EP-A-323841, EP-A-324377, EP-A-420237, EP-A-43983, EP-A-459136, EP-A-475206, EP-A-502314, EP-A-504888, EP-A-514198, WO 91/14679, WO 93/20816, US 4,355,040 and US 4,880,804. Preferred ARBs are the

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approved compounds candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan and valsartan, pharmaceutically acceptable salts thereof as well as ARBs not yet approved for pharmaceutical use. Of these the free acid of telmisartan or the sodium salt of telmisartan are particularly preferred. However, the
 5 invention applies equally to all ARBs other than the free acid of telmisartan or its sodium salt.

Examples of suitable excipients (adjuvants) are mannitol, sorbitol, xylitol, saccharose, calcium carbonate, calcium phosphate, lactose, croscarmellose sodium salt (cellulose carboxymethylether sodium salt, cross linked), crospovidone, sodium starch
 10 glycolate, hydroxypropylcellulose (low substituted), maize starch, polyvinylpyrrolidone, copolymers of vinylpyrrolidone with other vinyl derivatives (copovidones), hydroxypropyl cellulose, hydroxypropylmethyl cellulose, microcrystalline cellulose or starch, magnesium stearate, sodium stearyl fumarate, talc, hydroxypropylmethylcellulose, carboxymethylcellulose, cellulose acetate
 15 phthalate, polyvinylacetate, water, water/ethanol, water/glycerine, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetyl stearyl alcohol, carboxymethylcellulose or substances containing fat such as hard grease.

The various excipients are usually included for different purposes. Thus, the list of excipients comprises

- 20 • Inert diluents such as mannitol, sorbitol, xylitol, saccharose, calcium carbonate, calcium phosphate and lactose
- Disintegrants such as croscarmellose sodium salt (cellulose carboxymethylether sodium salt, cross linked), crospovidone, sodium starch glycolate, hydroxypropylcellulose (low substituted) and maize starch

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- Binders such as polyvinylpyrrolidone, copolymers of vinylpyrrolidone with other vinyl derivatives (copovidones), hydroxypropyl cellulose, hydroxypropylmethyl cellulose, microcrystalline cellulose or starch
 - Lubricants such as magnesium stearate, sodium stearyl fumarate and talc
- 5
- Agents for delaying release such as hydroxypropylmethyl cellulose, carboxymethyl cellulose, cellulose acetate phthalate and polyvinyl acetate and
 - Dyes acceptable for pharmaceutically use such as ferric oxides

The amount of ARB in a single dosage form is usually in the range of 10-800 mg. Depending on the ARB used preferred ranges are 150-300 mg (e.g. irbesartan), 60-90 mg (e.g. valsartan or telmisartan), 30-60 mg (e.g. telmisartan or losartan) or 15-30 mg (e.g. candesartan).

Particularly preferred are 80-85 mg, 40-45 mg or 20-25 mg. The amount of chlorthalidone in
5 a single dosage form is usually in the range of 10-15 mg or 20-30 mg, preferably 12-13 mg or 24-26 mg.

To produce a pharmaceutical preparation according to the invention such as a tablet for oral administration procedures known in the art can be used. Suitable excipients for the
10 compression of ARBs with chlorthalidone after mixing are sorbitol and magnesiumstearat, which can be replaced by other excipients such as mannitol or saccharose. Occasionally the properties of tablets can be modified by granulation of an active ingredient with selected excipients before final compression of all the components of the pharmaceutical preparation. For this purpose the ARB or salt thereof can be mixed, for example, with mannitol,
15 hydroxypropyl cellulose and, optionally, a coloring agent in a suitable blender. The resulting blend is preferably sieved and can be subjected to a dry granulation process in a roller compactor. The mentioned excipients might be replaced by other adjuvants such as lactose or microcrystalline cellulose. The resulting granulate is mixed with chlorthalidone and other excipients such as mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium
20 separate and optionally a coloring agent before being compressed to tablets. Alternatively, adjuvants such as lactose or croscarmellose sodium salt can be used.

It is often preferred that a fixed dose combination dosage form comprising an ARB and chlorthalidone shows fast dissolution and immediate drug release combined with adequate
25 stability. In case mere combination of the active ingredients is not practical due to incompatibilities with excipients used in the mono-dosage form of the active ingredients, it is possible to coat chlorthalidone particles in a fluidized-bed granulator with a polymer solution containing water soluble polymers like hydroxypropyl-cellulose, hydroxypropylmethylcellulose or polyvinylpyrrolidone, thereby reducing the contact surface
30 area of the chlorthalidone particles with the other components of the dosage form.

If this approach does not allow to stabilize the dosage form to a degree sufficient to achieve an acceptable shelf life or, due to the gel-forming properties of the polymer coat, slows the dissolution of chlorthalidone to an unacceptable rate, it is possible to produce separate film-coated tablets for the ARB and chlorthalidone in such a size and shape that these can be filled
5 into a capsule. By dividing the doses into two to four single small tablets for the ARB and into one or two small tablets for chlorthalidone, a capsule of size 1 to 0 long can be filled.

If this approach, due to a lag-time effect of the large capsule shells, reduces the drug dissolution rate of the ARB too much or, with regard to patients' compliance, a zero long
10 capsule is considered unreliable, it is possible to manufacture bilayer pharmaceutical tablets comprising a first layer containing the ARB in a pharmaceutical tablet base formulation having immediate release (fast dissolution) characteristics that readily dissolves in a physiological aqueous medium (dissolving tablet matrix), and a second layer containing chlorthalidone in a pharmaceutical tablet base
15 formulation having immediate release characteristics that readily swells and disintegrates in a physiological aqueous medium (disintegrating tablet matrix). The composition of a bilayer tablet can be chosen such that it facilitates dissolution of the drug at a physiological pH level and provides for immediate release of chlorthalidone from the fast disintegrating matrix. At the same time, a bilayer tablet structure can reduce stability problems caused by an
20 incompatibility of chlorthalidone with constituents of an ARB formulation.

The dissolving tablet matrix of the first tablet layer may have acidic, neutral or basic properties, a basic tablet matrix being preferred. In such preferred embodiments, the dissolving matrix comprises a basic agent, a water-soluble diluent and, optionally, other
25 excipients (adjuvants). Specific examples of suitable basic agents are alkali metal hydroxides such as NaOH and KOH; basic amino acids such as arginine and lysine; and meglumine (N-methyl-D-glucamine), NaOH and meglumine being preferred.

Specific examples of suitable water-soluble diluents are carbohydrates such as monosaccharides like glucose; oligosaccharides like sucrose, anhydrous lactose and lactose
30 monohydrate; and sugar alcohols like sorbitol, mannitol, dulcitol, ribitol and xylitol. Sorbitol is a preferred diluent.

Other excipients (adjuvants) are, for instance, selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers, specific examples of which are given below in connection with the second tablet layer composition. The excipients and/or adjuvants for the first tablet layer composition are preferably chosen such that a non-acidic, fast dissolving tablet matrix is obtained.

Other (optional) constituents may, for instance, be chosen from one or more of the following excipients and/or adjuvants in the amounts indicated:

10 10 to 30 wt.%, preferably 15 to 25 wt.%, of binders, carriers and fillers, thereby replacing the water-soluble diluent;

0.1 to 5 wt.%, preferably 0.5 to 3 wt.%, of lubricants;

0.1 to 5 wt.%, preferably 0.3 to 2 wt.%, of flow control agents;

1 to 10 wt.%, preferably 2 to 8 wt.%, of crystallization retarders;

15 1 to 10 wt.%, preferably 2 to 8 wt.%, of solubilizers;

0.05 to 1.5 wt.%, preferably 0.1 to 0.8 wt.%, of coloring agents;

0.5 to 10 wt.%, preferably 2 to 8 wt.%, of pH control agents;

0.01 to 5 wt.%, preferably 0.05 to 1 wt.%, of surfactants and emulsifiers.

20 The fast disintegrating tablet matrix of the second tablet layer composition may comprise a filler, a binder, a disintegrant and, optionally, other excipients (adjuvants). The filler is preferably selected from anhydrous lactose, spray-dried lactose and lactose monohydrate.

The binder is selected from the group of dry binders and/or the group of wet granulation

25 binders, depending on the manufacturing process chosen for the second tablet layer. Suitable dry binders are, for example, cellulose powder and microcrystalline cellulose. Specific examples of wet granulation binders are corn starch, polyvinyl pyrrolidone (Povidon), vinylpyrrolidone-vinylacetate copolymer (Copovidone) and cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl-cellulose and

30 hydroxypropylmethylcellulose.

Suitable disintegrants are, e.g., sodium starch glycolate, Crospovidon, Croscarmellose, sodium carboxymethylcellulose and dried corn starch, sodium starch glycolate being preferred.

The other excipients and adjuvants, if used, are preferably selected from diluents and carriers
5 such as cellulose powder, microcrystalline cellulose, cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, dibasic calcium phosphate, corn starch, pregelatinized starch, polyvinyl pyrrolidone (Povidone) etc.; lubricants such as stearic acid, magnesium stearate, sodium stearyl fumarate, glycerol tribehenate, etc.; flow control agents such as colloidal silica,
10 talc, etc.; crystallization retarders such as Povidone, etc.; solubilizers such as Pluronic, Povidone, etc.; coloring agents, including dyes and pigments such as Iron Oxide Red or Yellow, titanium dioxide, talc, etc.; pH control agents such as citric acid, tartaric acid, fumaric acid, sodium citrate, dibasic calcium phosphate, dibasic sodium phosphate, etc.; surfactants and emulsifiers such as Pluronic, polyethylene glycols, sodium carboxymethyl cellulose,
15 polyethoxylated and hydrogenated castor oil, etc.; and mixtures of two or more of these excipients and/or adjuvants.

For example, bilayer tablets of telmisartan can be produced with a method comprising the steps of:

- 20 (i) providing a first tablet layer composition by
- a) preparing an aqueous solution of an ARB, at least one basic agent and, optionally, a solubilizer and/or a crystallization retarder;
 - b) spray-drying said aqueous solution to obtain a spray-dried granulate;
 - c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;
 - 25 d) mixing said premix with a lubricant to obtain a final blend for the first tablet layer;
 - e) optionally, adding other excipients (adjuvants) in any of steps a) to d);
- (ii) providing a second tablet layer composition by
- f) mixing and/or granulating chlorthalidone with the constituents of a disintegrating tablet matrix and, optionally, further excipients (adjuvants);
 - 30 g) admixing a lubricant to obtain a final blend for the second tablet layer;
- (iii) introducing the first or the second tablet layer composition in a tablet press;
- (iv) compressing said tablet layer composition to form a tablet layer;

- (v) introducing the other tablet layer composition into the tablet press; and
(vi) compressing both tablet layer compositions to form a bilayer tablet.

Chlorthalidone is usually employed as a fine-crystalline powder, optionally in fine-milled,
5 peg-milled or micronized form. For instance, the particle size distribution of chlorthalidone, as determined by the method of laser light scattering in a dry dispersion system (Sympatec Helos/Rodos, focal length 100 mm) is preferably as follows:

d_{10} : $\leq 20 \mu\text{m}$, preferably 2 to $10 \mu\text{m}$

d_{50} : 2 to $80 \mu\text{m}$, preferably 10 to $30 \mu\text{m}$

10 d_{90} : 5 to $150 \mu\text{m}$, preferably 40 to $80 \mu\text{m}$

The ARB is preferably dissolved and transformed into a substantially amorphous form, its initial crystal morphology and particle size being of little importance for the physical and biopharmaceutical properties of the bilayer tablet formulation obtained. It is however
15 preferred to remove agglomerates from the starting material, e.g. by sieving, in order to facilitate wetting and dissolution during further processing.

A bilayer tablet generally comprises 10-800 mg, preferably 20-100 mg of ARB (e.g. candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan or valsartan) and 6.25-50
20 mg, preferably 12.5-25 mg of chlorthalidone. Particularly preferred forms are bilayer tablets comprising about 20/12.5 mg, 40/12.5 mg, 80/12.5 mg, 160/12.5 mg, 20/25 mg, 40/25 mg, 80/25 mg and 160/25 mg of ARB such as candesartan, irbesartan, olmesartan, telmisartan or valsartan and chlorthalidone, respectively.

25 The first tablet layer composition generally comprises 3 to 50 wt.%, preferably 5 to 35 wt.%, of active ingredient; 0.25 to 20 wt.%, preferably 0.40 to 15 wt.%, of basic agent; and 30 to 95 wt.%, preferably 60 to 80 wt.% of water-soluble diluent.

The second tablet layer composition generally comprises 1.5 to 35 wt.%, preferably 2 to 15
30 wt.%, of active ingredient; 25 to 75 wt.%, preferably 35 to 65 wt.%, of filler; 10 to 40 wt.%, preferably 15 to 35 wt.%, of dry binder; 0.5 to 5 wt.%, preferably 1 to 4 wt.%, of wet granulation binder; and 1 to 10 wt.%, preferably 2 to 8 wt.%, of disintegrant. The other

excipients and adjuvants are generally employed in the same amount as in the first tablet layer composition.

For preparing the bilayer tablet according to the present invention, the first and second tablet layer compositions may be compressed in the usual manner in a bilayer tablet press, for example a high-speed rotary press in a bilayer tableting mode. However, care should be taken not to employ an excessive compression force for the first tablet layer. Preferably, the ratio of the compression force applied during compression of the first tablet layer to the compression force applied during compression of both the first and second tablet layers is in the range of from 1:10 to 1:2. For instance, the first tablet layer may be compressed at moderate force of 4 to 8 kN, whereas the main compression of first plus second layer is performed at a force of 10 to 20 kN. During bilayer tablet compression adequate bond formation between the two layers is achieved by virtue of distance attraction forces (intermolecular forces) and mechanical interlocking between the particles.

Bilayer tablets obtained release the active ingredients rapidly and in a largely pH-independent fashion, with complete release occurring within less than 90 min and release of the major fraction occurring within less than 30 min. The dissolution/ disintegration kinetics of the bilayer tablet may be controlled in different ways. For instance, both layers may dissolve/disintegrate simultaneously. Preferably, however, the second tablet layer containing chlorthalidone disintegrates first whereas the first tablet layer containing the ARB dissolves in parallel or subsequently.

With the following method of producing a bilayer tablet, which can be easily adapted for other combinations of chlorthalidone with ARBs such as candesartan, eprosartan, irbesartan, losartan, olmesartan, valsartan, and pharmaceutically acceptable salts thereof, particularly favourable dissolution/disintegration and drug release properties are achieved for a combination of chlorthalidone with telmisartan. Said method comprises

(i) providing a first tablet layer composition by

- a) preparing an aqueous solution of ARB, at least one basic agent and, optionally, a solubilizer and/or a crystallization retarder;
- b) spray-drying said aqueous solution to obtain a spray-dried granulate;

- c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;
- d) mixing said premix with a lubricant to obtain a final blend for the first layer;
- e) optionally, adding other excipients and/or adjuvants in any of steps a) to d);
- (ii) providing a second tablet layer composition by
 - 5 f) mixing and /or granulating chlorthalidone with the constituents of a disintegrating tablet matrix and, optionally, further excipients and/or adjuvants;
 - g) admixing a lubricant to obtain a final blend for the second tablet layer;
- (iii) introducing the first or the second tablet layer composition into a tablet press;
- (iv) compressing said tablet layer composition to form a tablet layer;
- 10 (v) introducing the other tablet layer composition into the tablet press; and
- (vi) compressing both tablet layer compositions to form a bilayer tablet.

In a preferred embodiment of this method, an aqueous alkaline solution of ARB is prepared by dissolving the active ingredient in purified water with the help of one or more basic agents
 15 like sodium hydroxide and meglumine. Optionally, a solubilizer and/or a recrystallization retarder may be added. The dry matter content of the starting aqueous solution is generally 10 to 40 wt.%, preferably 20 to 30 wt.%.

The aqueous solution is then spray-dried at room temperature or preferably at increased temperatures of, for instance, between 50 and 100°C in a co-current or counter current spray-
 20 drier at a spray pressure of, for instance, 1 to 4 bar. Generally speaking, the spray-drying conditions are preferably chosen in such a manner that a spray-dried granulate having a residual humidity of ≤ 5 wt.%, preferably ≤ 3.5 wt.%, is obtained in the separation cyclone. To that end, the outlet air temperature of the spray-drier is preferably kept at a value of between about 80°C and 90°C while the other process parameters such as spray pressure,
 25 spraying rate, inlet air temperature, etc. are adjusted accordingly.

The spray-dried granulate obtained is preferably a fine powder having the following particle size distribution:

- d_{10} : $\leq 20 \mu\text{m}$, preferably $\leq 10 \mu\text{m}$
- 30 d_{50} : $\leq 80 \mu\text{m}$, preferably 20 to 55 μm
- d_{90} : $\leq 350 \mu\text{m}$, preferably 50 to 150 μm

After spray-drying the ARB as well as the excipients contained in the spray-dried granulate are in a substantially amorphous state with no crystallinity being detectable. From a physical point of view, the spray-dried granulate containing telmisartan is a solidified solution or glass having a glass transition temperature T_g of preferably $> 50^\circ\text{C}$, more preferably $> 80^\circ\text{C}$.

5 Based on 100 parts by weight of ARB, the spray-dried granulate preferably contains 5 to 200 parts by weight of basic agent and, optionally, solubilizer and/or crystallization retarder.

The water-soluble diluent is generally employed in an amount of 30-95 wt.%, preferably 60-80 wt.%, based on the weight of the first tablet layer composition.

10 The lubricant is generally added to the premix in an amount of 0.1 to 5 wt.%, preferably 0.3 to 2 wt.%, based on the weight of the first tablet layer composition.

Mixing is carried out in two stages, i.e. in a first mixing step the spray-dried granulate and the diluent are admixed using, for example, a high-shear mixer or a free-fall blender, and in a second mixing step the lubricant is blended with the premix, preferably also under conditions of high shear. The method of the invention is however not limited to these mixing procedures and, generally, alternative mixing procedures may be employed in steps c), d), and also in the subsequent steps f) and g), such as, for example, container mixing with intermediate screening.

For direct compression, the second tablet layer composition may be prepared by dry-mixing the constituent components, for example by means of a high-intensity mixer or a free-fall blender. Alternatively and preferably, the second tablet layer composition is prepared using a wet granulation technique wherein an aqueous solution of a wet granulation binder is added to a premix and subsequently the wet granulate obtained is dried, e.g. in a fluidized-bed dryer or drying chamber. The dried mixture is screened and then a lubricant is admixed, for example using a tumbling mixer or free-fall blender, where after the composition is ready for compression.

For production of the bilayer tablet according to the present invention, the first and second tablet layer compositions are compressed in a bilayer tablet press, e.g. a rotary press in the bilayer tableting mode, in the manner described above.

30 According to the present invention ARBs and chlorthalidone are combined to produce pharmaceutical preparations for the treatment of hypertension, and treatment or prevention of cardiovascular events or stroke. Preferably, use of said combinations is indicated in

connection with hypertension, cardiac insufficiency (heart failure), ischemic peripheral circulatory disorders, myocardial ischemia, myocardial infarction, left ventricular hypertrophy, diabetic neuropathy, diabetic retinopathy, glaucoma, diabetic nephropathy, diseases of the bladder or gastrointestinal diseases. The combinations appear particularly
5 valuable to prevent, i.e. to reduce the risk of transient ischemic attacks, stroke, myocardial infarction, left ventricular hypertrophy, progression of cardiac insufficiency after cardiovascular events such as myocardial infarction, development of diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and any kind of cardiovascular death.

10 The following examples describe selected embodiments of the present invention. They illustrate the subject matter of the invention without restricting the scope of the technical features.

15 EXAMPLES

Example 1

In a first step the sodium salt of the ARB telmisartan, mannitol, red iron oxide and hydroxypropyl cellulose are mixed with a high-shear mixer. Subsequently magnesium
20 stearate, which has been passed through an 0.8 mm sieve, is added and the mixture subjected to a dry granulation process in a roller compactor.

In a parallel process step chlorthalidone is mixed with mannitol, microcrystalline cellulose, sodium starch glycolate and red iron oxide. Both the chlorthalidone mixture and the granules containing the sodium salt of telmisartan are passed through an 0.8 mm sieve, intermixed in a
25 free fall blender and finally mingled with magnesium stearate, which had been passed through an 0.8 mm sieve.

One obtains a pharmaceutical preparation which can be conveniently compressed to tablets showing a good solubility of the active ingredients. Using a suitable tablet press (e.g. Korsch EK0 or Fette P1200) produces tablets with the following composition, whereas the amount of
30 sodium salt of telmisartan corresponds to an amount of 80 mg of the free acid of telmisartan.

Constituents	mg/tablet	%tablet
Sodium salt of telmisartan	83.417	13.903
Chlorthalidone	12.500	2.083
Mannitol	336.483	56.081
Microcrystalline cellulose	120.000	20.000
Sodium starch glycolate	30.000	5.000
Red iron oxide	0.600	0.100
Hydroxypropylcellulose	5.000	0.833
Magnesiumstearate	12.000	2.000
Total	600.000	100.000

Similarly, the composition of the tablet can be described as follows:

Constituents	mg/tablet	%/tablet	%/granules
Sodium salt of telmisartan	83.417	13.903	83.417
Mannitol	10.983	1.831	10.983
Hydroxypropylcellulose	5.000	0.833	5.000
Red iron oxide	0.100	0.017	0.100
Magnesiumstearate	0.500	0.083	0.500
Total	100.000	16.667	100.000
Chlorthalidone	12.500	2.083	
Mannitol	325.500	54.250	
Microcrystalline cellulose	120.000	20.000	
Sodium starch glycolate	30.000	5.000	
Red iron oxide	0.500	0.083	
Magnesiumstearate	11.500	1.917	
Total	600.000	100.000	

The tablets show the following features:

5 Size: 16.2 x 7.9 mm (r=5.86 mm)

Weight: 598.7 mg $\pm$ 0.22 %

Thickness: on the average 6.16 mm

Example 2

Chlorthalidone, the sodium salt of telmisartan, sorbitol and red iron oxide are mixed in a free fall blender, passed through a 0.8 mm sieve, and processed to a powder after the addition of magnesium stearate. Using a suitable tablet press (e.g. Korsch EK0 or Fette P1200) tablets of,

5 the following composition are obtained, whereas the amount of sodium salt of telmisartan corresponds to an amount of 80 mg of the free acid of telmisartan.

Constituents	mg/tablet	%tablet
Sodium salt of telmisartan	83.417	13.903
Chlorthalidone	12.500	2.083
Sorbitol	494.483	82.414
Red iron oxide	0.600	0.100
Magnesiumstearate	9.000	1.500
Total	600.000	100.000

Typical features of the tablets are:

10 Size: 16.2 x 7.9 mm (r=5.86 mm)

Weight: 600.7 mg $\pm$ 0.34 %

Thickness: durchschnittlich 5.96 mm

Example 3

Constituents		mg / 1.684 mg SD granulate	volatile constituent	kg / batch
(01)	Telmisartan	1.000		45.000
(02)	Sodium hydroxide	0.084		3.780
(03)	Povidone K 25	0.300		13.500
(04)	Meglumine	0.300		13.500
(05)	Purified water		5.000	(225.000)
		1.684	5.000	75.780

1. Spray solution

225.000 kg of purified water are measured into a suitable stainless steel vessel at a temperature of between 20-40°C. In sequence, 3.780 of kg sodium hydroxide, 45.000 kg of telmisartan (mixture of polymorph A and B), 13.500 kg of Povidone K 25 and 13.500 kg of meglumine are dissolved in the purified water under intensive stirring until a virtually clear, slightly yellowish, alkaline solution is obtained.

2. Spray drying

The solution is sprayed into a suitable spray dryer, e.g. a Niro P 6.3 equipped with Schlick atomizing nozzles of 1.0 mm diameter, with a flow-through heating coil connected upstream of the dryer, and dried to give a white to off-white fine granulate. The spray mode is counter-current at a spray-pressure of about 3 bar, an inlet air temperature of about 125°C and a spray rate of about 11 kg/h, thus resulting in an outlet air temperature of about 85°C. The temperature of the flow through heating coil water bath is set at a temperature of about 80°C.

3. Protective Screening

The dry granulate powder is screened through a screen of 0.5 mm mesh size, e.g. using a Vibra Sieve machine.

The resulting amorphous telmisartan spray-dried granulate is further processed to the first layer of a bilayer tablet composition similar to example 4.

Example 4

	Constituents	mg/tablet 1st layer	mg/SD granulate	mg/tablet 2nd layer
(01)	Telmisartan SD granulate consisting of (02) to (06):	67.360		
(02)	Telmisartan		40.000	
(03)	Sodium hydroxide		3.360	
(04)	Polyvidone		12.000	
(05)	Meglumine		12.000	
(06)	Purified water		264.000*	
(07)	Sorbitol P/6	168.640		
(08)	Magnesium stearate, screened	4.000		1.000
(09)	Chlorthalidone			12.500
(10)	Microcrystalline cellulose			64.000
(11)	Red iron oxide			0.330
(12)	Sodium starch glycolate			4.000
(13)	Lactose monohydrate fine, screened			112.170
(14)	Maize starch, dried at 45 °C			6.000
		240.000	67.360	200.000

* 200 mg in SD granulate, 64 mg in granulation liquid of chlorthalidone granulate

1. Final blend A

- 5 168.640 kg of sorbitol are mixed with 67.360 kg of telmisartan spray dried granulate in a suitable high shear mixer, e.g. Diosna P 600, for 4 minutes using both impeller and chopper. Next 4.0 kg of magnesium stearate are added to the resulting pre-mix and admixed in the high shear mixer for further 30 seconds.

10 2. Final blend B

9.000 kg of purified water of about 70°C are transferred to a suitable mixing vessel, 6.000 kg of maize starch, dried at 45°C, are suspended in the water. This suspension is stirred into 55.000 kg of purified water of about 90°C using e.g. an Ekato stirrer.

Next, 112.170 kg of lactose monohydrate, 12.500 kg of chlorthalidone, 64.000 kg of microcrystalline cellulose (Avicel PH 101), 0.330 kg of red iron oxide and 4.000 kg of sodium starch glycolate are mixed in a suitable high shear granulator, e.g. Diosna P 600, until homogeneous, and moistened with 70.000 kg of the above-prepared aqueous granulating liquid.

Process parameters for wet granulation:

Process step	Duration (min)	Impeller (setting)	Chopper (setting)
Pre-mixing	3	1	1
Moistening	2	1	1
Wet mixing	4	2	2
Emptying	About 0.5	1	0

After moistening, the resulting wet granulate is dried in a suitable fluid bed dryer, e.g. Glatt WSG 120 at an inlet air temperature of 100°C, an inlet air flow of 2000-3000 m³/h until a product temperature of about 55°C is reached.

The dry granulate is screened to reduce the particle size using a suitable screening machine, e.g. a Comil screen machine equipped with a rasp screen of 2 mm mesh size.

Finally 1.000 kg of pre-screened magnesium stearate are admixed to the screened granulate material and mixed in a suitable tumbling mixer, e.g. a Lerner rotating spike mixer, for 100 revolutions at a speed of 8-10 rpm.

3. Bilayer tablet compression

Using a suitable rotary tablet press, 240 kg of the final blend (A) and 200 kg of the final blend (B) are compressed into bilayer tablets. The target weight for the first layer is 240 mg, the target weight for the second layer is 200 mg.

Process parameters for tableting:

Tablet press	Fette 3090	
Tabletting speed	100.000 (80.000 – 120.000) tablets/h	
Stirrer blade speed:	1st layer about 30 rpm	2nd layer about 75 rpm
Compression force	5 (4 – 6) KN	12 (10 – 14) KN

As a rule, the tablet hardness is adjusted by variation of the main compression force of the second layer.

5

The resulting bilayer tablets have the following characteristics:

Shape / diameter	oval, both faces convex / 14 x 6.8 mm
Colour	first layer: white to off-white second layer: red
Weight	440 mg (total) 240 mg (layer 1: with telmisartan) 200 mg (layer 2: with chlorthalidone)
Thickness	about 5.2 mm

Example 5

	Constituents	mg/tablet 1st layer	mg/SD granulate	mg/tablet 2nd layer
(01)	Telmisartan SD granulate consisting of (02) to (06):	67.360		
(02)	Telmisartan		40.000	
(03)	Sodium hydroxide		3.360	
(04)	Polyvidone		12.000	
(05)	Meglumine		12.000	
(06)	Purified water		(200.000)	
(07)	Sorbitol P/6	168.640		
(08)	Magnesium stearate, screened	4.000		1.000
(09)	Chlorthalidone			25.000
(10)	Microcrystalline cellulose			64.000
(11)	Yellow iron oxide			0.330
(12)	Sodium starch glycolate			4.000
(13)	Lactose monohydrate fine			105.67
		240.000	67.360	200.000

Manufacturing is carried out as in Example 3. Instead of the wet granulation process described in Example 2, the second layer composition is manufactured by dry mixing of (09) to (13) in a suitable free fall blender, e.g. a 1 m³ container mixer, for 200 revolutions at a speed of 10 rpm. Then, (08) is admixed to the main mixture for further 50 revolutions in the container mixer. In order to achieve a homogenous distribution of the color pigment, an additional premix with yellow iron oxide and a portion of the microcrystalline cellulose, e.g. 2.000 kg, which is screened through an 0.8 mm mesh screen manually before transfer to the main mixture, may be performed. The resulting bilayer tablets display virtually the same physical characteristics as described in example 3, except for the color.

Example 6

Composition of Telmisartan/Chlorthalidone Bilayer Tablets (mg per tablet):

Ingredient	40/12.5 mg	80/12.5 mg
Telmisartan layer		
Telmisartan	40.000	80.000
Sodium hydroxide	3.360	6.720
Povidone	12.000	24.000
Meglumine	12.000	24.000
Purified water*	(200.000)	(400.000)
Sorbitol	168.640	337.280
Magnesium stearate	4.000	8.000
Total telmisartan layer	240.000	480.000
Chlorthalidone layer		
Chlorthalidone	12.500	12.500
Lactose monohydrate	112.170	112.170
Microcrystalline Cellulose	64.000	64.000
Corn starch	6.000	6.000
Red iron oxide	0.330	0.330
Sodium starch glycolate	4.000	4.000
Purified water*	(64.000)	(64.000)
Magnesium stearate	1.000	1.000
Total Chlorthalidone layer	200.000	200.000
Total tablet weight	440.000	680.000

*Does not appear in final product

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CLAIMS:

1. A pharmaceutical composition comprising chlorthalidone and angiotensin II receptor blocker telmisartan.
2. The pharmaceutical composition of claim 1, further comprising one or
5 more pharmaceutically acceptable excipients.
3. The pharmaceutical composition of claim 2 for oral administration.
4. The pharmaceutical composition of claim 2 or 3, wherein the one or more excipients are selected from the group consisting of: mannitol, sorbitol, xylitol, saccharose, calcium carbonate, calcium phosphate, lactose, croscarmellose sodium
10 salt, crospovidone, sodium starch glycolate, hydroxypropylcellulose, maize starch, polyvinylpyrrolidone, copolymers of vinylpyrrolidone with other vinyl derivatives, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, microcrystalline cellulose or starch, magnesium stearate, sodium stearyl fumarate, talc, hydroxypropylmethylcellulose, carboxymethylcellulose, cellulose acetate phthalate,
15 polyvinylacetate, water, water/ethanol, water/glycerine, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetyl stearyl alcohol, carboxymethylcellulose and substances containing fat.
5. The pharmaceutical composition of claim 4, wherein the croscarmellose sodium salt is crosslinked cellulose carboxymethylether sodium salt.
- 20 6. The pharmaceutical composition of claim 4, wherein the hydroxypropylcellulose is low substituted.
7. The pharmaceutical composition of claim 4, wherein the copolymers of vinylpyrrolidone with other vinyl derivatives are copovidones.
8. The pharmaceutical composition of claim 4, wherein the fat is hard
25 grease.

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9. The pharmaceutical composition of any one of claims 1 to 8, wherein the angiotensin II receptor blocker is telmisartan sodium salt.

10. A method of producing the pharmaceutical composition of any one of claims 2 to 9, comprising mixing the chlorthalidone and the angiotensin II receptor
5 blocker telmisartan with the one or more pharmaceutically acceptable excipients.

11. The method of claim 10, wherein the resulting pharmaceutical composition prepared by the method is an oral dosage form.

12. The method of claim 11, wherein the oral dosage form is a tablet.