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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING BOSENTAN

(57) Abstract: The present invention relates to a stable solid pharmaceutical composition comprising or consisting of bosentan or a pharmaceutically acceptable salt thereof, a first diluent or filler which is a cellulose derivative and a second diluent or filler which is different from the first diluent as well as a process for manufacturing the inventive pharmaceutical composition.



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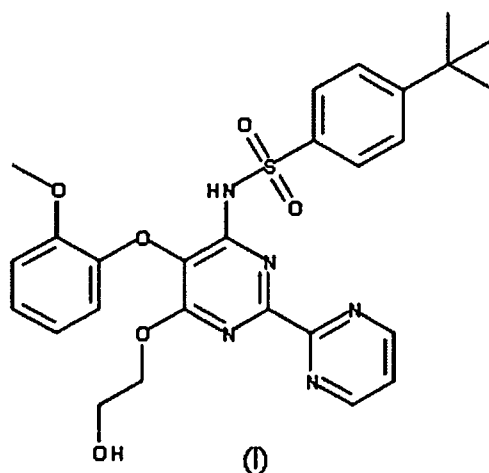
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**Pharmaceutical composition comprising bosentan**

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The present invention relates to a solid pharmaceutical composition comprising bosentan or a pharmaceutically acceptable salt thereof, a process for manufacturing the inventive composition and use of the inventive pharmaceutical composition.

- 10 Bosentan, represented by structural formula (I) and chemically named 4-*tert*-butyl-*N*-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]benzenesulfonamide, is a dual endothelin receptor antagonist with affinity for both endothelin ET<sub>A</sub> and ET<sub>B</sub> receptors thereby preventing the deleterious effects of ET-1. It is useful for the treatment of cardiovascular disorders such as hypertension, ischaemia, vasospasm and angina pectoris.



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- Bosentan and the preparation thereof is disclosed in EP 526 708 A1. It is marketed as Tracleer® and it is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and it is indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. Bosentan is commercial  
20 available as 62.5 mg or 125 mg film-coated tablets as well as 32 mg dispersible tablet.

The commercial available film-coated tablets have the following composition: bosentan (125

or 62.5 mg), maize starch, pregelatinized starch, sodium starch glycolate, povidone, glycerol dibehenate and magnesium stearate, while the coating is composed of hypromellose, glycerol triacetate, talc, titanium dioxide, yellow and red iron oxides, and ethyl cellulose (taken from the Summary of Products Characteristics (SmPC) of Tracleer®, available in the internet from the website of the European Medicines Agency (EMA): URL: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000401/WC500041597.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000401/WC500041597.pdf)). According to the SmPC, these tablets have a shelf life of 4 years, but they also exhibit a storage condition that it is not allowed to store the tablets above 30°C.

The bosentan tablets are manufactured using a typical wet granulation method which comprises (i) dry blending of bosentan monohydrate, maize starch, pregelatinized starch, sodium starch glycolate, and povidone; (ii) wet granulation with purified water in a high shear granulator to obtain granules; (iii) subsequent fluid bed drying, sieving, and mixing with glycerol dibehenate and magnesium stearate; and (iv) compressing into tablets and coating (taken from the EPAR - Scientific Discussion of Tracleer®, available in the internet from the website of the EMA: URL: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Scientific\\_Discussion/human/000401/WC500041457.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000401/WC500041457.pdf)).

According to the SmPC, the commercial dispersible bosentan tablet contains 32 mg bosentan, microcrystalline cellulose, calcium hydrogen phosphate anhydrous, croscarmellose sodium, anhydrous colloidal silica, tartaric acid, tutti frutti flavour, aspartame, acesulfame potassium and magnesium stearate. The dispersible tablet has also a storage condition; it is prohibited to store it above 25°C.

WO 2006/123285 discloses in example 1 the composition of commercial Tracleer® dispersible tablets and in example 2 and 3 further dispersible tables which comprise bosentan and suitable excipients, which are fillers, disintegrants, glidants, acidifying agents, flavouring agents, sweetening agents, and lubricants.

The pharmaceutical compositions comprising bosentan which are known in the state of the art are labelled with storage conditions. It is not allowed to store the film-coated bosentan tablets above 30°C and the dispersible bosentan tablets have to be stored below 25°C. Such storage conditions are in general a great disadvantage for the commercialization of pharmaceutical compositions, e.g. tablets, as temperature controlled manufacturing, transport and storage is necessary. Furthermore the storage at a certain temperature is a burden for the patient in need of such pharmaceutical compositions, particularly in tropical or sub-tropical climate zones.

The present inventors have carried out stability studies with commercially available Tracleer® 125 mg film-coated tablets for a period of up to 7.5 months. Thereby it was observed that Tracleer® 125 mg film-coated tablets show a time dependent drop in drug dissolution (profile), i.e. a retarded drug release, over time. The tested Tracleer® tablets showed after 7.5 months of storage about 16 % (after 15 minutes), about 13 % (after 30 mins), and about 13 % (after 45 mins) less dissolution of bosentan in comparison to initial dissolution. Such a time dependent drop in dissolution (profile) or retarded drug release is unfavourable from pharmaceutical point of view and leads according to the applicable pharmaceutical guidelines, at least, to the declaration of a storage condition (as occurred in case of the commercially available Tracleer® tablets) or, in the worst case, to the restriction of the shelf life.

Therefore there is a need for alternative pharmaceutical compositions comprising or consisting of bosentan or a pharmaceutically acceptable salt thereof with increased stability. Furthermore there is a need for alternative pharmaceutical compositions comprising or consisting of bosentan or a pharmaceutically acceptable salt thereof with a stable dissolution profile over time; i.e. the tablets show after storage, e.g. at accelerated conditions for up to 6 months, no significant change or drop in dissolution (profile) of bosentan and/or no significantly retarded release of bosentan.

According to relevant pharmaceutical regulatory guidelines, like the guidelines from the International Conference on Harmonisation (ICH) (e.g. Q1A(R2) - Stability Testing of New Drug Substances and Products) or the European Medicines Agency (EMA) (e.g. CPMP/QWP/609/96/Rev 2 – Guideline on Declaration of Storage Conditions), storage conditions are necessary, when a deterioration of the properties of a pharmaceutical composition, e.g. a tablet, is noticeable during stability studies under controlled storage conditions, i.e. the pharmaceutical composition is not stable. The major attributes which affect the properties or the physical and chemical stability of a pharmaceutical composition are e.g. appearance, hardness (or resistance to crushing), disintegration time, dissolution (profile), friability, water content, chemical stability (degradation products, so-called related substances), and uniformity of dosage units or mass. A significant change of at least one of these attributes over the time under controlled storage conditions could lead to the requirement of storage conditions. In general, a "significant change" for a drug product is defined mostly as either a 5 % change from its initial value or failure to meet an acceptance criteria. Especially significant changes or deterioration of the attributes of chemical stability (i.e. increased degradation products), disintegration time of the tablet, or drug dissolution (profile) have a high impact.

Therefore there it was an object of the present invention to provide a stable solid pharmaceutical composition comprising bosentan or a pharmaceutically acceptable salt thereof, characterized in that the stable solid pharmaceutical composition having a less strict storage condition or no storage condition.

- 5 In this context increased stability means that the inventive composition has a less strict storage condition or no storage condition. Accordingly, it was an object of the present invention to provide such a stable pharmaceutical composition comprising bosentan.

Furthermore it was an object of the present invention to provide a stable pharmaceutical composition comprising bosentan which does not show after storage, e.g. at accelerated  
10 conditions for up to 6 months, an increased amount of degradation products, a deterioration of the disintegration time of the tablet and/or a deteriorated dissolution profile of the drug bosentan. In particular it was an object of the present invention to provide a stable pharmaceutical composition comprising bosentan or a pharmaceutically acceptable salt thereof with a stable dissolution profile over time; i.e. the tablets show after storage, e.g. at  
15 accelerated conditions for up to 6 months, no significant drop in dissolution (profile) or no significantly retarded release of bosentan.

The object of the present invention has been solved by the subject matter as defined in the claims.

It was surprisingly found that the stability of a solid pharmaceutical composition comprising  
20 bosentan or a pharmaceutically acceptable salt thereof is increased, if the composition comprises a combination of two different diluents or fillers, whereby the first diluent or filler is a cellulose derivative.

Stability studies (under conditions of 40 °C and 75 % relative humidity for a period of up to 7.5 months), which were carried out with solid pharmaceutical compositions according to the  
25 present invention, confirm the stability of the inventive composition and show that drug dissolution, in contrast to the commercially available film-coated bosentan tablets Tracleer®, do not significantly change during storage; e.g. the tablets show after storage no significant drop in dissolution of bosentan.

Accordingly, the first aspect of the present invention is a solid pharmaceutical composition  
30 comprises or consists of bosentan or a pharmaceutically acceptable salt thereof, a first diluent or filler which is a cellulose derivative and a second diluent or filler, which is different from the first diluent and which is an organic diluent, e.g. an organic diluent selected from carbohydrates, modified carbohydrates and starches.

In the context of the present invention the inventive pharmaceutical composition can be present in all solid dosage forms which are compressed, including optionally coated tablets as film-coated tablets, (oro)dispersible tablets, modified-release tablets and gastro-resistant tablets. Preferably, the inventive composition is suitable for oral administration and is coated with a suitable coating. Accordingly, the most preferred composition is a coated or film-coated tablet.

In context of the present invention bosentan can be used as the free base or in form of a pharmaceutically acceptable salt (also commonly referred to as bosentan), preferably in form of the free base. Furthermore, bosentan can be used in anhydrous or in hydrate form, preferably bosentan is used in the monohydrate form. Furthermore, the particle size distribution of bosentan in the inventive composition is preferably such, that 90 wt.-% of bosentan particles have a particle size of less than 150  $\mu\text{m}$  ( $D(v,0.9) < 150 \mu\text{m}$ ). More preferably the particle size distribution has a  $D(v,0.9) < 100 \mu\text{m}$ , more preferably a  $D(v,0.9) < 50 \mu\text{m}$ , and most preferably a  $D(v,0.9) < 30 \mu\text{m}$ . Preferably, the particle size distribution is further characterized in that 50 wt.-% of the bosentan particles have a particle size of less than 50  $\mu\text{m}$  ( $D(v,0.5) < 50 \mu\text{m}$ ). More preferably the particle size distribution has a  $D(v,0.5) < 30 \mu\text{m}$ , more preferably a  $D(v,0.5) < 15 \mu\text{m}$ , and most preferably a  $D(v,0.9) < 10 \mu\text{m}$ .

Bosentan is present in the inventive pharmaceutical composition in a therapeutically effective amount. In a preferred embodiment the amount of bosentan, calculated as the percentage of the content in weight of the free base, based on the total weight of the uncoated composition, e.g. tablet, is 15 % to 75 %, preferably between 30 % to 60 %, and more preferably 45 % to 55 %. In particular the amount of bosentan as active ingredient is about 50 %. In a most preferred embodiment of the present invention, the amount of bosentan in the inventive dosage form is 32 mg, 62.5 mg or 125 mg calculated on the free base.

Examples of cellulose derivative as first diluent or filler contained in the inventive solid pharmaceutical composition are microcrystalline cellulose, powdered cellulose, silicified cellulose, cellulose acetate and celluloses which are co-processed with one or more pharmaceutical acceptable excipient. In a preferred embodiment the first diluent is microcrystalline cellulose.

As second diluent, which is different from the first diluent, preferably an organic diluent is used, e.g. an organic diluent selected from carbohydrates, modified carbohydrates and starches, but also inorganic diluents, like calcium or magnesium carbonate, calcium sulfate, kaolin, and magnesium oxide, are applicable. Examples of the second diluent or filler contained in the inventive composition are glucose (synonym is dextrose), lactose

(anhydrous or monohydrate), maltose, sucrose, isomalt, lactitol, maltitol, mannitol, sorbitol, xylitol, starch (maize, potato, wheat), pregelatinized starch, dextrin, and the like. The second diluent is preferably lactose (anhydrous or monohydrate) or starch (maize, potato, wheat).

5 The solid pharmaceutical composition according to the present invention, e.g. a tablet or film-coated tablet, contains amongst bosentan or a pharmaceutically acceptable salt thereof, first diluent and second diluent further pharmaceutical excipients as diluent or filler, binder, disintegrant, glidant and lubricant. These pharmaceutical excipients may be contained in the powder mixture (dry mix) and/or in the extragranular phase. In a preferred embodiment of the invention the granulate contains bosentan, a cellulose derivative as first diluent, at least one  
10 additional diluent, at least one binder and optionally one disintegrant, while lubricants and optionally glidants and are contained as extragranular components only. More preferably at least one disintegrant is contained in addition as extragranular component.

Examples of the binder contained in the solid pharmaceutical composition according to the invention include methyl cellulose (MC), hydroxypropylmethyl cellulose (hypromellose, HPMC), hydroxypropyl cellulose (hyprollose, HPC), carboxymethylcellulose sodium (CMC sodium), maltodextrin, polyethylene glycol (PEG), maltodextrin, polyvinylpyrrolidone (povidone, PVP), vinylpyrrolidone/vinyl acetate copolymer (copovidone), and polyvinyl alcohol/polyethylene glycol graft copolymer (Kollicoat® IR), and the like. In a preferred embodiment the binder is povidone or HPMC.

20 Examples of the disintegrant, which may be contained in the granulate and/or as an extragranular component, are croscarmellose sodium, sodium starch glycolate, polyvinylpolypyrrolidone (crospovidone), low-substituted hydroxypropyl cellulose (L-HPC), and the like. Preferably the disintegrant is sodium starch glycolate or low-substituted hydroxypropyl cellulose. As glidants, colloidal (anhydrous) silica, talc and the like may be  
25 used, while magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, magnesium silicate, magnesium trisilicate and hydrogenated vegetable oil are examples of suitable lubricants. Preferably colloidal (anhydrous) silica is used as glidant. The lubricant is preferably magnesium stearate or sodium stearyl fumarate.

30 A second aspect of the present invention relates to a process for manufacturing of the solid pharmaceutical composition according to the present invention. The wet granulation process known from the prior art, which is disclosed in the scientific discussion of Tracleer®, is a fairly time-consuming and not quite efficient process, as bosentan and four additional excipients have to be sieved and blended. In addition, such a multi-stage process may lead to insufficient physical parameters and it may also affect the final quality of the pharmaceutical

composition. When following the disclosed process, the present inventors observed indeed sticking during tablet compression, i.e. the tableting mixture stuck to the punches.

On the other hand, the direct compression process disclosed in WO 2006/123285: mixing six different excipients of phase II for 10-20 minutes; adding this mixture to phase I, which is a mixture of bosentan and two further excipients, and re-mixing again for 10-20 minutes; adding of phase III and mixing 2-5 minutes; and subsequent compression into tablets; is also a quite complex and time consuming process.

Accordingly, another object of the present invention was to provide a simple, (cost) efficient, and robust process for manufacturing a pharmaceutical composition, preferably an optionally coated tablet as film-coated tablet, comprising bosentan. This object was solved by a process for manufacturing the solid pharmaceutical composition according to the present invention by granulation which comprises the following steps:

- i) preparing a granulate from a powder mixture (dry mix) comprising bosentan or a pharmaceutically acceptable salt thereof, a first diluent which is a cellulose derivative, a second diluent which is different from the first diluent and which is an organic diluent, such as lactose, and pharmaceutically acceptable excipients;
- ii) preparing a tableting mixture comprising the granulate obtained in step (i) and optionally pharmaceutically acceptable excipients;
- iii) compressing the tableting mixture; and optionally
- iv) applying a film coating to the tablet core obtained in step (iii).

In a particularly preferred form, the granulate in step (i) is produced by means of wet granulation, whereby water, an alcohol such as ethanol or isopropanol, and mixtures of the aforementioned solvents may be used as a granulation liquid. Moreover, the granulation liquid may optionally contain a binder, e.g. polyvinylpyrrolidone, copovidone, hydroxypropylmethyl cellulose or hydroxypropyl cellulose. Preferably wet granulation is conducted in a rapid mixer granulator or a fluid bed processor.

In an alternative embodiment, the granulate in step (i) is produced by means of dry granulation technique readily known to a person skilled in the art. Preferably roller compactors, Fitzpatrick roller compactor mills and tableting machines can be used.

In a particularly preferred form, the inventive composition contains one or more disintegrants in the intragranular phase (step (i)) and/or extragranular phase (step (ii)), preferably in the

intragranular and extragranular phase. The reason for this is that it has been found that the dissolution rate of the active ingredient bosentan in an aqueous medium is increased if an extragranular disintegrant is present. Preferably the disintegrant is croscarmellose sodium, sodium starch glycolate, polyvinylpolypyrrolidone, or low-substituted hydroxypropyl cellulose.

- 5 The most preferred disintegrants are low-substituted hydroxypropyl cellulose, e.g. LH-31 or LH-32 which are fine grades, and sodium starch glycolate.

Alternatively, the present invention relates to a direct compression process for manufacturing the inventive solid pharmaceutical composition comprising the steps of:

- 10 i) providing a powder mixture (dry mix) comprising bosentan or a pharmaceutically acceptable salt thereof, a first diluent which is a cellulose derivative, a second diluent which is different from the first diluent and which is an organic diluent, such as lactose, and pharmaceutically acceptable excipients;
- ii) compressing the powder mixture, and optionally
- iii) applying a film coating to the tablet core obtained in step (ii).

- 15 In both processes, namely granulation and direct compression, fillers or diluents, binders, disintegrants, glidants, and lubricants as set out hereinbefore may be used as pharmaceutically acceptable excipients.

- In a preferred embodiment of the invention, the solid pharmaceutical composition additionally comprises a pharmaceutically acceptable coating. Suitable inert coating agents and methods
- 20 for coating particles or granules are well known in the art. Typically, inert coating agents comprise an inert film-forming agent dispersed in a suitable solvent, and may further comprise other pharmaceutically acceptable excipients, such as colorants and/or plasticizers. Preferably, the coating of the inventive composition comprises one or more of the following film forming components: hydroxypropyl cellulose, hydroxypropylmethyl cellulose, ethyl
- 25 cellulose, polyvinyl alcohol, polyvinyl alcohol/polyethylene glycol graft copolymer, sugar, or mixtures thereof. As colorants aluminium lakes, such as indigo carmine aluminium lake, and/or iron oxides, such as red iron oxide, and/or titanium dioxide are preferably used in suitable amounts.

- According to the present invention, the amount of the first diluent or filler in the solid
- 30 pharmaceutical composition may vary within a range of 10 to 60 %, in particular 20 to 40 % in weight based on the total weight of the uncoated composition. The amount of second diluent may vary within a range of 2 to 35 %, in particular 8 to 20 % in weight based on the

total weight of the uncoated composition. The amount of binder may vary within a range of 0.5 to 15 %, in particular 1 to 5 % in weight based on the total weight of the uncoated composition. The amount of disintegrant may vary within a range of from 0.5 to 20%, in particular 2 to 10 % in weight based on the total weight of the uncoated composition. The amount of glidant may vary within ranges of from 0.1 to 5 %, in particular 0.5 to 2.5 % in weight based on the total weight of the uncoated composition. The amount of lubricant may vary from 0.1 to 5 %, preferably from 0.1 to 3.0 %.

The properties or the physical and chemical stability of the solid pharmaceutical composition of the invention may be tested in conventional manner, e.g. by measurement of appearance, hardness (or resistance to crushing), disintegration time, dissolution, friability, water content, assay for bosentan and/or its degradation products (related substances), and/or uniformity of dosage units or mass after storage at controlled storage conditions; e.g. at long term and/or accelerated conditions according to ICH guideline Q1A(R2) (i.e. at 25 °C / 60 % relative humidity (RH) and/or at 40 °C / 75 % RH). These tests shall be performed according to applicable pharmaceutical regulatory standards as described e.g. in ICH or EMA guidelines and/or the European Pharmacopoeia (EP).

At least some of these attributes, i.e. properties or physical and chemical stability, preferably most of these attributes and most preferably all of these attributes of the inventive composition are stable over time and different controlled storage conditions. In a preferred embodiment the dissolution (profile) of the solid pharmaceutical composition according to the present invention, e.g. a tablet or film-coated tablet, is stable over at least 6 months when stored at long term or accelerated storage conditions, i.e. 25 °C / 60 % RH or 40 °C / 75 % RH. A stable dissolution profiles over time does not show a significant, e.g. more than 5%, change or drop in drug dissolution after storage. More preferably, dissolution and further additional attributes such as, e.g., assay, related substances or uniformity of dosage units or mass are stable after storage over at least 6 months when stored at long term or accelerated storage conditions. By "stable" is meant that a measured value is within a narrow range of values which are set before in a specification according to a regulatory guideline, e.g. the European Pharmacopoeia or the ICH guideline. In most cases said narrow range of values is interpreted in accordance to the definition of a "significant change" and therefore it is a range of  $\pm 5$  % from an initial value (i.e. a range from initial value minus 5 % to initial value plus 5 %).

The solid pharmaceutical composition of the present invention, for example, a tablet or film-coated tablet, may vary in shape and be, e.g., round, oval, oblong, cylindrical, caplet shaped or any other suitable shape, preferably it is round or caplet shaped. Furthermore the composition according to the invention may be scored or engraved.

The solid pharmaceutical composition of the present invention, for example, a tablet or film-coated tablet, has a diameter ranging between 3.5 and 15 mm and most preferably between 5.5 and 7.0 mm for round tablets and the dimension of a caplet is between 9.0 x 3.0 mm and 17.0 x 7.5 mm, preferably it is 12.7 x 5.9 mm. Thickness is ranging from 2.0 to 5.0 mm, preferably between 2.5 and 4.6 mm.

The solid pharmaceutical composition according to the present invention has a suitable hardness (or resistance to crushing), preferably the film-coated tablets may have a hardness (or resistance to crushing) from 50 N to 130 N, preferably 85 N to 110 N.

Furthermore the composition of the invention, for example, a tablet or a film-coated tablet, may be coloured and/or marked so as to impart an individual appearance and to make them instantly recognizable. The use of dyes can serve to enhance the appearance as well as to identify the pharmaceutical composition. Dyes suitable for use in pharmacy typically include carotinoids, iron oxides or chlorophyll. The pharmaceutical composition of the invention, for example, a tablet or a film-coated tablet, may be marked using an imprint code.

The inventive pharmaceutical composition may be packed in any conventional packaging known in the art, for example blisters, polypropylene or polyethylene (e.g. HDPE, high density polyethylene) containers or glass bottles. Preferably the composition is packed in a blister known in the art, e.g. sealed aluminium blister (Alu-Alu), Aluminium / Aluminium peel-push blisters or PVC/PE/PVDC/aluminium-blisters.

A third aspect of the present invention relates to the use of the solid pharmaceutical composition according of the present invention in the manufacture of a medicament for use in the treatment of pulmonary arterial hypertension. The inventive composition is preferably used in the treatment or prophylaxis of pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension, systemic sclerosis, and idiopathic pulmonary fibrosis.

In a preferred embodiment, the solid pharmaceutical composition according to the present invention is used in the treatment or prophylaxis of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class II, III, and IV. In a more preferred embodiment the solid pharmaceutical composition according to the present invention is used in the treatment or prophylaxis of primary (idiopathic and familial) PAH, secondary PAH associated with scleroderma without significant interstitial pulmonary disease, or PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology. Furthermore, in a preferred embodiment the solid pharmaceutical composition according to the present invention is used to reduce the number of new digital

ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

The following examples are intended to further illustrate the present invention.

Examples:

| Ingredients in (mg/tablet)                               | E1            | E2            | E3            | E4            | E5            | E6            |
|----------------------------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| <b>Stage A (Dry mix)</b>                                 |               |               |               |               |               |               |
| Bosentan monohydrate                                     | 133.88        | 133.52        | 129.08        | 133.52        | 129.08        | 129.08        |
| Microcrystalline cellulose<br>(Comprecel® M 101 D+)      | 61.62         | 68.98         | 83.42         | 58.98         | 73.42         | 68.67         |
| Isomalt (Galen IQ 800)                                   | 28.00         | -             | -             | -             | -             | -             |
| Pregelatinized starch<br>(Starch 1500®)                  | -             | 20.00         | -             | -             | -             | -             |
| Lactose monohydrate<br>(Granulac® 200)                   | -             | -             | 20.00         | 40.00         | -             | -             |
| Maize starch                                             | -             | -             | -             | -             | 20.00         | 18.00         |
| Low-substituted hydroxypropyl<br>cellulose (L-HPC LH-31) | -             | 10.00         | 10.00         | 10.00         | 10.00         | 10.00         |
| Sodium starch glycolate type - A<br>(Primojel®)          | 8.00          | -             | -             | -             | -             | -             |
| <b>Stage B (Binder Solution)</b>                         |               |               |               |               |               |               |
| Povidone (Plasdone® K-29/32)                             | 10.00         | 5.00          | 5.00          | 5.00          | 5.00          | 10.00         |
| Purified water                                           | q.s.          | q.s.          | q.s.          | q.s.          | q.s.          | q.s.          |
| <b>Stage C (Blending and Lubrication)</b>                |               |               |               |               |               |               |
| Low-substituted hydroxypropyl<br>cellulose (L-HPC LH-31) | -             | 10.00         | -             | -             | 10.00         | 10.00         |
| Sodium starch glycolate type – A<br>(Primojel®)          | 6.00          | -             | -             | -             | -             | -             |
| Magnesium stearate                                       | 2.50          | 2.50          | 2.50          | 2.50          | 2.50          | 3.00          |
| Colloidal anhydrous silica<br>(Aerosil® 200)             | -             | -             | -             | -             | -             | 1.25          |
| <b>Core tablet weight (mg)</b>                           | <b>250.00</b> | <b>250.00</b> | <b>250.00</b> | <b>250.00</b> | <b>250.00</b> | <b>250.00</b> |
| <b>Stage D (Coating)</b>                                 |               |               |               |               |               |               |
| Instamoistshield Pink A21E00132                          | 8.00          | 8.00          | 12.00         | 8.00          | 8.00          | 8.00          |
| Isopropanol                                              | q. s.         | q. s.         | q. s.         | q. s.         | q. s.         | q. s.         |
| Purified water                                           | q. s.         | q. s.         | q. s.         | q. s.         | q. s.         | q. s.         |
| <b>Coated tablet weight (mg)</b>                         | <b>258.00</b> | <b>258.00</b> | <b>262.00</b> | <b>258.00</b> | <b>258.00</b> | <b>258.00</b> |

Instamoistshield Pink A21E00132 is composed of hypromellose, glycerine, ethyl cellulose, talc, titanium dioxide, iron oxide yellow and iron oxide red.

Process:

- 1) Sift all the ingredients of stage A separately,
- 2) blend the sifted material in a rapid mixer granulator low impeller speed,
- 3) prepare binder solution of stage B by dissolving povidone in purified water,
- 5 4) granulate the dry mix in rapid mixer granulator using binder solution of stage B,
- 5) mill the wet mass,
- 6) load the wet mass in fluidized bed dryer and dry it,
- 7) sift the dried granules and all the stage C ingredients separately,
- 8) blend the extra-granular material with granules in blender,
- 10 9) compress the tablets on rotary tablet compression machine,
- 10) prepare coating solution of stage D by dispersing coating material in isopropanol and/or purified water, and
- 11) coat the tablets using perforated coating machine.

| <b>Ingredients in (mg/tablet)</b>                     | <b>E7</b>     |
|-------------------------------------------------------|---------------|
| <b>Stage A (Dry mix)</b>                              |               |
| Bosentan monohydrate                                  | 133.88        |
| Microcrystalline cellulose (Comprecel® M 102 D+)      | 39.37         |
| Pregelatinized starch (Starch 1500®)                  | 37.00         |
| Low-substituted hydroxypropyl cellulose (L-HPC LH-31) | 25.00         |
| Magnesium stearate                                    | 1.25          |
| <b>Stage B (Blending and Lubrication)</b>             |               |
| Low-substituted hydroxypropyl cellulose (L-HPC LH-31) | 11.00         |
| Magnesium stearate                                    | 1.25          |
| Colloidal anhydrous silica (Aerosil® 200)             | 1.25          |
| <b><i>Core tablet weight (mg)</i></b>                 | <b>250.00</b> |
| <b>Stage C (Coating)</b>                              |               |
| Instamoistshield Pink A21E00132                       | 8.00          |
| Isopropyl alcohol                                     | q. s.         |
| Purified water                                        | q. s.         |
| <b><i>Coated tablet weight (mg)</i></b>               | <b>2.00</b>   |

Instamoistshield Pink A21E00132 is composed of hypromellose, glycerine, ethyl cellulose, talc, titanium dioxide, iron oxide yellow and iron oxide red.

Process:

- 1) Sift all the ingredients of stage A separately,
- 2) blend all the sifted material in a blender,
- 5 3) compact the blend to form slugs,
- 4) mill the slugs to granules,
- 5) sift the granules and all the stage B ingredients separately,
- 6) blend the extra-granular material of stage B with granules in a blender,
- 7) compress the tablets on rotary tablet compression machine,
- 10 8) prepare coating solution of stage C by dispersing coating material in isopropanol and/or purified water, and
- 9) coat the tablets using perforated coating machine.

Two batches of the solid pharmaceutical compositions according to the present invention in form of film-coated tablets are produced according to formulation E3 (hereinafter referred to as E3a and E3b). The film-coated tablets of formulations E3a and E3b as well as Tracleer® 125 mg film-coated tablets (batch no. BW029A02; manufacturer: Actelion Pharmaceuticals Deutschland GmbH; packaging material: PVC/PE/PVDC/aluminium-blisters) are used to carry out stability studies under conditions of 40 °C and 75 % relative humidity (RH) for up to 7.5 months (accelerated storage conditions, ICH guideline Q1A(R2)).

Dissolution of bosentan (drug release in percent [%] after 15, 30, and 45 minutes (mins); in acetate buffer pH 4.5 + 1 % sodium lauryl sulfate (SLS) as medium; apparatus: paddle; speed: 75 rpm, volume: 900 ml; according to European Pharmacopoeia (EP) 7.3, section 2.9.3) of the film-coated tablets of the inventive compositions E3a and E3b as well as Tracleer® 125 mg film-coated tablets are measured initially (in the following initially), this means for E3a and E3b directly after production, and when stored in PVC/PE/PVDC/aluminium-blisters after storage time of 1, 2, 3, 6, or 7.5 months (in the following 1M, 2M, 3M, 6M, or 7.5M):

| Tracleer® 125 mg |                 |         |         |
|------------------|-----------------|---------|---------|
| Time point       | Dissolution [%] |         |         |
|                  | 15 mins         | 30 mins | 45 mins |
| Initial          | 92              | 100     | 101     |
| 1M               | 91              | 99      | 100     |
| 2M               | 82              | 91      | 97      |
| 3M               | 80              | 89      | 96      |
| 6M               | 77              | 91      | 96      |
| 7.5M             | 76              | 87      | 88      |

| Time point | E3a             |         |         | E3b             |         |         |
|------------|-----------------|---------|---------|-----------------|---------|---------|
|            | Dissolution [%] |         |         | Dissolution [%] |         |         |
|            | 15 mins         | 30 mins | 45 mins | 15 mins         | 30 mins | 45 mins |
| Initial    | 97              | 98      | 98      | 96              | 99      | 100     |
| 1M         | 97              | 97      | 98      | 94              | 99      | 99      |
| 2M         | 100             | 102     | 102     | 98              | 100     | 101     |
| 3M         | 101             | 101     | 102     | 94              | 99      | 101     |
| 6M         | 102             | 104     | 104     | -               | -       | -       |

Claims:

1. Solid pharmaceutical composition comprising bosentan or a pharmaceutically acceptable salt thereof, a first diluent which is a cellulose derivative and a second diluent which is different from the first diluent and which is an organic diluent, such as lactose.
- 5 2. Solid pharmaceutical composition according to claim 1, wherein bosentan is in the monohydrate form.
3. Solid pharmaceutical composition according to claim 1 or 2, wherein the bosentan is contained in an pharmaceutical active amount, preferably 32 mg, 62.5 mg or 125 mg.
- 10 4. Solid pharmaceutical composition according to any one of claims 1 to 3, wherein 90 wt.-% of bosentan particles have a particle size of less than 150  $\mu\text{m}$ .
5. Solid pharmaceutical composition according to any one of claims 1 to 4, wherein the solid pharmaceutical composition is a tablet.
6. Solid pharmaceutical composition according to any of the preceding claims obtainable by using the method of granulation.
- 15 7. Solid pharmaceutical composition according to claim 6 obtainable by using the method of wet granulation.
8. Solid pharmaceutical composition according to any one of claims 6 or 7, wherein the composition contains one or more disintegrants in the extragranular phase.
9. Solid pharmaceutical composition according to any of the preceding claims, wherein the  
20 first diluent is microcrystalline cellulose.
10. Solid pharmaceutical composition according to any of the preceding claims, wherein the second diluent is starch or lactose.
11. Solid pharmaceutical composition according to any of the preceding claims, wherein the second diluent is maize starch or lactose monohydrate.
- 25 12. A process for manufacturing a solid pharmaceutical composition according to anyone of the preceding claims, comprising the steps of:
  - i) preparing a granulate from a powder mixture (dry mix) comprising bosentan or a pharmaceutically acceptable salt thereof, a first diluent which is a cellulose

derivative, a second diluent which is different from the first diluent and which is an organic diluent, such as lactose, and pharmaceutically acceptable excipients;

ii) preparing a tableting mixture comprising the granulate obtained in step (i) and optionally pharmaceutically acceptable excipients;

5       iii) compressing the tableting mixture; and optionally

iv) applying a film coating to the tablet core obtained in step (iii).

13. Process according to claim 12, wherein the granules are prepared by granulation, preferably by wet granulation.

10       14. Process according to claim 13, wherein the tableting mixture obtained in step (ii) contains one or more disintegrants in the extragranular phase.

15. Use of a solid pharmaceutical composition according of any one of claims 1 to 11 for the use in the manufacture of a medicament for use in the treatment of pulmonary arterial hypertension.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2012/001522

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61K9/20 A61K9/28 A61P9/12  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 July 2012

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08/08/2012

Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2012/001522

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/001522

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