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(54) **Title**: PHARMACEUTICAL COMPOSITION COMPRISING N-[3-CHLORO-4-(3-FLUOROBENZYLOXY)PHENYL]-6-[5({[2-(METHYLSULFONYL)ETHYL]AMINO}METHYL)-2-FURYL]QUINAZOLIN-4-AMINE OR A PHARMACEUTICALLY ACCEPTABLE SALT, SOLVATE OR SOLVATED SALT THEREOF

(57) **Abstract**: The present invention relates to a pharmaceutical composition comprising N-[3-chloro-4-(3-fluorobenzyloxy)phenyl]-6-[5({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]quinazolin-4-amine or a pharmaceutically acceptable salt, solvate or solvated salt thereof, and a process for preparing the pharmaceutical composition.

Pharmaceutical composition comprising N-[3-chloro-4-(3-fluorobenzyloxy)phenyl]-6-[5({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]quinazolin-4-amine or a pharmaceutically acceptable salt, solvate or solvated salt thereof

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising N-[3-chloro-4-(3-fluorobenzyloxy)phenyl]-6-[5({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]quinazolin-4-amine or a pharmaceutically acceptable salt, solvate or solvated salt thereof, and a process for preparing the pharmaceutical composition.

BACKGROUND OF THE INVENTION

N-[3-chloro-4-(3-fluorobenzyloxy)phenyl]-6-[5({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]quinazolin-4-amine is hereinafter referred to as lapatinib in accordance with the international non-proprietary name (INN) given by the World Health Organization (WHO). Lapatinib ditosylate monohydrate was shown to act as an inhibitor of the intracellular tyrosine kinase domains of certain epidermal growth factor receptors, such as ErbB-1 and ErbB-2, and is currently used in the treatment of patients with breast cancer, whose tumours overexpress ErbB-2.

WO 2006/113649 discloses oral pharmaceutical compositions comprising an active ingredient, which is for example lapatinib or a salt or solvate thereof, together with a binder, and optionally a disintegrant and a lubricant.

WO 2010/023187 discloses pharmaceutical compositions comprising lapatinib or a pharmaceutically acceptable salt thereof as active pharmaceutical ingredient, wherein the active pharmaceutical ingredient is present in an amount of more than 60% by weight based on the total weight of the composition.

WO 2010/023188 discloses pharmaceutical compositions comprising lapatinib or a pharmaceutically acceptable salt thereof wherein a unit dose of the composition contains 1200 to 1300 mg of the active pharmaceutical ingredient calculated as the free base.

SUMMARY OF THE INVENTION

It has now been found that a pharmaceutical composition comprising lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof, at least one binder, at least one disintegrant, at least one lubricant, and at least one filler, wherein the filler comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, is associated with advantages compared to prior art compositions. In particular, the pharmaceutical composition according to the present invention can be prepared in a cost and time efficient way, especially large scale manufacturing can be done at high speed without producing a significant number of defective products with regard to tablet weight and tablet appearance, whereby the pharmaceutical composition shows a desired dissolution behaviour.

DETAILED DESCRIPTION OF THE INVENTION

Lapatinib and the pharmaceutically acceptable salts, solvates and solvated salts thereof can be prepared as described in WO 99/35146 and WO 02/02552.

Lapatinib or the pharmaceutically acceptable salt or solvate or solvated salt thereof is preferably present in the pharmaceutical composition according to the present invention in an amount of from 30 to 60% by weight, relative to the weight of the pharmaceutical composition, more preferably in an amount of from 40 to 60% by weight, relative to the weight of the pharmaceutical composition.

Preferably, the pharmaceutical composition according to the present invention contains 250 mg, 500 mg, 750 mg, 1000 mg or 1250 mg of lapatinib or the pharmaceutically acceptable salt or solvate or solvated salt thereof (calculated as the free base). Most preferably, the pharmaceutical composition according to the present invention contains 250 mg of lapatinib or the pharmaceutically acceptable salt or solvate or solvated salt thereof (calculated as the free base).

Pharmaceutically acceptable salts of lapatinib include, for example, the hydrochloride, hydrobromide, sulfate, nitrate, acetate, tartrate, citrate, fumarate, lactate, malate, maleate, mesylate, pamoate, oxalate, gluconate, salicylate, benzoate, succinate, and tosylate salts.

Preferred pharmaceutically acceptable salts of lapatinib include the monomesylate, the dimesylate, the monotosylate and the ditosylate salt, in particular the ditosylate anhydrate salt. The pharmaceutically acceptable solvates of lapatinib include the hydrates of lapatinib. The monohydrate of lapatinib is particularly preferred. Pharmaceutically acceptable solvated salts of lapatinib include lapatinib mesylate monohydrate, lapatinib dimesylate monohydrate, lapatinib tosylate monohydrate, and lapatinib ditosylate monohydrate. Lapatinib ditosylate monohydrate is most preferred.

In a preferred embodiment, the pharmaceutical composition of the present invention comprises a binder selected from the group consisting of gelatine, polyvinyl pyrrolidone (PVP), polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC) and combinations thereof.

The binder is preferably present in the pharmaceutical composition of the present invention in an amount of from 1 to 20% by weight, relative to the weight of the pharmaceutical composition, preferably in an amount of from 5 to 10% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof.

Crospovidone is a cross-linked polyvinylpyrrolidone. It is formed by so-called popcorn-polymerization of vinylpyrrolidone. Examples of crospovidone include Kollidon CL, Kollidon CL-M, PolyKoVidone, Polyplasdone XL and Polyplasdone XL-10. A preferred example is Polyplasdone XL.

The disintegrant is preferably present in the pharmaceutical composition of the present invention in an amount of from 0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, preferably in an amount of from 4 to 6% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises a lubricant selected from the group consisting of magnesium stearate, calcium

stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof.

The lubricant is preferably present in the pharmaceutical composition of the present invention in an amount of from of 0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, preferably in an amount of from 0.5 to 2% by weight, relative to the weight of the pharmaceutical composition.

The microcrystalline cellulose is present in the pharmaceutical composition of the present invention in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition. Preferably, the microcrystalline cellulose has a median particle size of 50 to 100 µm. The particle size distribution is measured by laser diffraction on a Mastersizer 2000 with dry powder dispersion unit Scirocco 2000 (Measurement conditions: Sample weight is 1000 mg; the feed rate with a micro feed tray is 80%; the dispersion pressure is 2 bar; the diffraction method is Frauenhofer with analysis model "general purpose" and refraction index of particles is 0.000; measurement time is 12 s; background time is 12 s).

In a preferred embodiment, the pharmaceutical composition of the present invention comprises mannitol, more preferably in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises calcium hydrogen phosphate. The calcium hydrogen phosphate may be present in the form of calcium hydrogen phosphate anhydrate or calcium hydrogen phosphate dihydrate. In a particularly preferred embodiment, the pharmaceutical composition of the present invention comprises calcium hydrogen phosphate in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises lactose. In a particularly preferred embodiment, the pharmaceutical composition of the present invention comprises lactose in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition. The lactose can be present as alpha-lactose

anhydrate, alpha-lactose monohydrate, beta-lactose, amorphous lactose, crystalline lactose or mixtures thereof. Alpha-lactose monohydrate is most preferred.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises starch. The starch is, for example, maize starch, wheat starch, rice starch and/or potato starch, and can be present as natural starch and/or pre-treated starch, such as pregelatinized starch or thermally treated starch. In a particularly preferred embodiment, the pharmaceutical composition of the present invention comprises the starch in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
at least one binder selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
at least one disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
at least one lubricant selected from the group consisting of magnesium stearate, calcium stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
at least one binder selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
at least one disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
at least one lubricant selected from the group consisting of magnesium stearate, calcium

stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
at least one binder selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
at least one disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
at least one lubricant selected from the group consisting of magnesium stearate, calcium stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of the pharmaceutical composition, of at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
at least one binder selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
at least one disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;

at least one lubricant selected from the group consisting of magnesium stearate, calcium stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and lactose in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
a binder selected from the group consisting of polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
a binder selected from the group consisting of polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;

at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
a binder selected from the group consisting of polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of the pharmaceutical composition, of at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
a binder selected from the group consisting of polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;

at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and lactose in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
a binder selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylmethylcellulose and combinations thereof;
a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium and combinations thereof;
a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
a filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of the pharmaceutical composition, of at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
lapatinib ditosylate monohydrate,
a binder selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylmethylcellulose and combinations thereof;
a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium and combinations thereof;
a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
a filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of the pharmaceutical composition, of lactose.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
30 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
1 to 20% by weight, relative to the weight of the pharmaceutical composition, of at least one binder selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, of at least one disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, of at least one lubricant selected from the group consisting of magnesium stearate, calcium stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
30 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
1 to 20% by weight, relative to the weight of the pharmaceutical composition, of at least one binder selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, of at least one disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, of at least one lubricant selected from the group consisting of magnesium stearate, calcium stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium

arachinate, calcium arachinate, and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of the pharmaceutical composition, of at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
30 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
1 to 20% by weight, relative to the weight of the pharmaceutical composition, of at least one binder selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, of at least one disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, of at least one lubricant selected from the group consisting of magnesium stearate, calcium stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and lactose in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
30 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
1 to 20% by weight, relative to the weight of the pharmaceutical composition, of a binder selected from the group consisting of polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;

0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, of a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, of a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
30 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
1 to 20% by weight, relative to the weight of the pharmaceutical composition, of a binder selected from the group consisting of polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, of a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, of a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of the pharmaceutical composition, of at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
30 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,

1 to 20% by weight, relative to the weight of the pharmaceutical composition, of a binder selected from the group consisting of polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, of a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, of a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
at least one filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and lactose in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises
30 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof,
1 to 20% by weight, relative to the weight of the pharmaceutical composition, of a binder selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylmethylcellulose and combinations thereof;
0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, of a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium and combinations thereof;
0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, of a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
a filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of the pharmaceutical composition, of lactose.

In a further preferred embodiment, the pharmaceutical composition of the present invention comprises

40 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib ditosylate monohydrate,
5 to 10% by weight, relative to the weight of the pharmaceutical composition, of a binder selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylmethylcellulose and combinations thereof;
4 to 6% by weight, relative to the weight of the pharmaceutical composition, of a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium and combinations thereof;
0.5 to 2% by weight, relative to the weight of the pharmaceutical composition, of a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
a filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of the pharmaceutical composition, of lactose.

The pharmaceutical composition of the present invention can further comprise a glidant, for example, colloidal silicon dioxide.

The pharmaceutical composition of the present invention can further comprise a colorant, for example, ferric oxide.

The pharmaceutical composition according to the present invention is preferably a tablet or coated tablet. More preferably, the pharmaceutical composition according to the present invention is a coated tablet.

The coating may comprise for example a cellulose, such as hydroxypropylmethylcellulose, a polyethylene glycol, such as Macrogol 400, a sorbitan fatty acid ester, such as Polysorbate 80, and/or titanium dioxide. Optionally, the coating may comprise a colorant, such as ferric oxide or an aluminum lake (e.g. sunset yellow aluminum lake E110). Commercially available coating compositions, such as Opadry coating compositions (e.g. Opadry® YS-1-13065-A) can be used.

The pharmaceutical composition according to the present invention can be prepared by a process comprising a wet granulation step. Examples of wet granulation include wet granulation in a swaying granulator, high shear wet granulation, and fluidized bed granulation. High shear wet granulation is preferred.

The pharmaceutical composition according to the present invention can be produced by a process comprising:

(a) granulating a mixture comprising lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof, a filler, and optionally a disintegrant, using an aqueous solution of the binder as granulation liquid;
(b) drying the granules obtained in step (a);
(c) mixing the dried granules with the lubricant, and optionally the disintegrant;

provided that the disintegrant is added in step (a) and/or (c).

If the pharmaceutical composition according to the present invention is a tablet or coated tablet, the process may comprise an additional step of compressing the mixture obtained in step (c) into tablets.

Preferably, the granules are dried to a water content of not more than 3% by weight, more preferably of from 0.5 to 3% by weight, in above step (b). The water content can be determined as described in Ph. Eur. 7.0 by measuring the loss on drying (determined on 1 g of the granules dried in an oven at 105°C for 3 h).

A preferred process for preparing the pharmaceutical composition according to the present invention includes the following steps:
A dry blend of lapatinib or the pharmaceutically acceptable salt or solvate or solvated salt thereof, the filler and a part of the disintegrant (optionally all sieved before through a Frewitt 1.0 mm sieve) is filled into a wet granulator, such as a Glatt VG 25 granulator. The binder is dissolved in a suitable amount of purified water and then added to the dry blend under continuous stirring. Wet granulation is preferably performed at a temperature of from 20 to 30°C. The wet granules are then dried in a fluidized bed dryer, such as a Glatt GPCG 3/5 dryer, preferably at a temperature of from 30 to 40°C. The granules are sieved, e.g. through a Frewitt 1.0 mm sieve, and blended for 5 to 10 minutes in a turbula mixer at 25 rpm with the remaining part of the disintegrant. The lubricant, preferably after having been sieved through

a 0.5 mm sieve, is added to the resulting blend, and the final blend is mixed in a turbula mixer at 25 rpm for 1 to 5 minutes. The final blend is compressed into tablets, for example in a Kilian RTS 24 tablet press. Optionally, the tablets are coated, for example in a Glatt Mini coater (0.8 l drum) using a suitable film-coating preparation, for example Opadry® YS-1-13065-A.

Another preferred process for preparing the pharmaceutical composition according to the present invention includes the following steps:
A dry blend of lapatinib or the pharmaceutically acceptable salt or solvate or solvated salt thereof, the filler and a part of the disintegrant (optionally all sieved before through a Frewitt 1.0 mm sieve) is filled into a fluid-bed-granulator, such as a Glatt GPCG 3/5 granulator. The binder is dissolved in a suitable amount of purified water. Fluid-bed-granulation is started and the binder solution sprayed on top of the dry blend (e.g. through a 1.0 mm spraying nozzle) preferably at a temperature of from 20 to 30°C. The wet granules are then dried in the fluid-bed-granulator preferably at a temperature of from 30 to 40°C. The granules are sieved, e.g. through a Frewitt 1.0 mm sieve, and blended for 5 to 10 minutes in a turbula mixer at 25 rpm with the remaining part of the disintegrant (optionally sieved before through a Frewitt 1.0 mm sieve). The lubricant, preferably after having been sieved through a 0.5 mm sieve, is added to the resulting blend and the final blend is mixed in a turbula mixer at 25 rpm for 1 to 5 minutes. The final blend is compressed into tablets, for example in a Kilian RTS 24 tablet press. Optionally, the tablets are coated, for example in a Glatt Mini coater (0.8 l drum) using a suitable film-coating preparation, for example Opadry® YS-1-13065-A.

The pharmaceutical composition according to the present invention optionally comprises a coating. The coating can be prepared by

(i) suspending the components of the coating in water, an organic solvent (for example ethanol) or a mixture of water and an organic solvent (for example a water/ethanol mixture),
(ii) coating the pharmaceutical composition with the thus obtained suspension using a suitable coating device, for example a fluid-bed-coater or a pan coater, and
(iii) drying the coated pharmaceutical composition.

The pharmaceutical composition of the present invention may be useful in the treatment of cancer including breast cancer, ovarian cancer, brain cancer, head cancer, neck cancer,

gastric cancer, colorectal cancer, prostate cancer, bladder cancer or prostate cancer. The pharmaceutical composition of the present invention may further be useful in the treatment of psoriasis.

The pharmaceutical composition of the present invention can comprise a further active ingredient selected from anti-neoplastic agents, such as paclitaxel, docetaxel, gemcitabine, irinotecan, topotecan, cisplatin, carboplatin, oxaliplatin, capecitabine, anastrozole, letrozole, pazopanib, imatinib, erlotinib, dasatinib, sorafenib, sunitinib and gefitinib.

EXAMPLES

Example 1

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
Polyvinyl pyrrolidone	7.5
Sodium starch glycolate	5.5
Microcrystalline cellulose	22.6
Magnesium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

Each of the lapatinib ditosylate monohydrate, microcrystalline cellulose and sodium starch glycolate are sieved through a Frewitt 1.0 mm sieve. A dry blend of the sieved lapatinib ditosylate monohydrate, the sieved microcrystalline cellulose and half of the sieved sodium starch glycolate is filled into a wet granulator (Glatt, VG 25 granulator). The polyvinyl pyrrolidone is dissolved in purified water (5 parts per weight of water per 1 part per weight of polyvinyl pyrrolidone) and then added to the dry blend under continuous stirring. Wet granulation is performed at 20°C. The wet granules are then dried in a fluidized bed dryer (Glatt, GPCG 3/5) at 35°C. The granules are sieved through a Frewitt 1.0 mm sieve and blended for 10 minutes in a turbula mixer at 25 rpm with the second half of the sieved sodium starch glycolate. Magnesium stearate is added to the resulting blend after having been

sieved through a 0.5 mm hand sieve and the blend thus obtained is mixed in a turbula mixer at 25 rpm for 3 minutes. The final blend is compressed into tablets using a Kilian RTS 24 tablet press. The tablets are coated in a Glatt Mini coater (0.8 l drum) using a the commercially available Opadry® YS-1-13065-A film coating.

Example 2

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
Polyvinyl pyrrolidone	7.5
Sodium starch glycolate	5.5
Microcrystalline cellulose	22.6
Calcium behenate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 1 with the exception that calcium behenate is used in place of magnesium stearate.

Example 3

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
Polyvinyl pyrrolidone	7.5
Sodium starch glycolate	5.5
Microcrystalline cellulose	22.6
Calcium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 1 with the exception that calcium stearate is used in place of magnesium stearate.

Example 4

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
HPMC	7.5
Sodium starch glycolate	5.5
Microcrystalline cellulose	22.6
Magnesium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 1 with the exception that HPMC is used in place of polyvinyl pyrrolidone.

Example 5

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
Polyvinyl pyrrolidone	7.5
Croscarmellose sodium	5.5
Microcrystalline cellulose	22.6
Magnesium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 1 with the exception that croscarmellose sodium is used in place of sodium starch glycolate.

Example 6

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
HPMC	7.5
Croscarmellose sodium	5.5
Microcrystalline cellulose	22.6
Magnesium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 1 with the exception that HPMC is used in place of polyvinyl pyrrolidone and croscarmellose sodium is used in place of sodium starch glycolate.

Example 7

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
Polyvinyl pyrrolidone	7.5
Sodium starch glycolate	5.5
Microcrystalline cellulose	12.6
Alpha-lactose monohydrate	10.0
Magnesium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

Each of the lapatinib ditosylate monohydrate, microcrystalline cellulose, alpha-lactose monohydrate and sodium starch glycolate are sieved through a Frewitt 1.0 mm sieve. A dry

blend of the sieved lapatinib ditosylate monohydrate, the sieved microcrystalline cellulose, the sieved alpha-lactose monohydrate and half of the sieved sodium starch glycolate is filled into a wet granulator (Glatt, VG 25 granulator). The polyvinyl pyrrolidone is dissolved in purified water (5 parts per weight of water per 1 part per weight of polyvinyl pyrrolidone) and then added to the dry blend under continuous stirring. Wet granulation is performed at 20°C. The wet granules are then dried in a fluidized bed dryer (Glatt, GPCG 3/5) at 35°C. The granules are sieved through a Frewitt 1.0 mm sieve and blended for 10 minutes in a turbula mixer at 25 rpm with the second half of the sieved sodium starch glycolate. Magnesium stearate is added to the resulting blend after having been sieved through a 0.5 mm hand sieve and the blend thus obtained is mixed in a turbula mixer at 25 rpm for 3 minutes. The final blend is compressed into tablets using a Kilian RTS 24 tablet press. The tablets are coated in a Glatt Mini coater (0.8 l drum) using a commercially available Opadry® YS-1-13065-A film coating.

Example 8

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
HPMC	7.5
Sodium starch glycolate	5.5
Microcrystalline cellulose	12.6
Alpha-lactose monohydrate	10.0
Magnesium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 7 with the exception that HPMC is used in place of polyvinyl pyrrolidone.

Example 9

Component	Content in film-coated tablet

	[% by weight]
Lapatinib ditosylate monohydrate	60.0
Polyvinyl pyrrolidone	7.5
Croscarmellose sodium	5.5
Microcrystalline cellulose	12.6
Alpha-lactose monohydrate	10.0
Magnesium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 7 with the exception that croscarmellose sodium is used in place of sodium starch glycolate.

Example 10

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
HPMC	7.5
Croscarmellose sodium	5.5
Microcrystalline cellulose	12.6
Alpha-lactose monohydrate	10.0
Magnesium stearate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 7 with the exception that HPMC is used in place of polyvinyl pyrrolidone and croscarmellose sodium is used in place of sodium starch glycolate.

Example 11

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	60.0
HPMC	7.5
Croscarmellose sodium	5.5
Microcrystalline cellulose	12.6
Alpha-lactose monohydrate	10.0
Calcium behenate	1.4
Film coating	3.0

Total weight of film-coated tablet: 675 mg

The coated tablets are prepared as described in Example 7 with the exception that HPMC is used in place of polyvinyl pyrrolidone, croscarmellose sodium is used in place of sodium starch glycolate, and calcium behenate is used in place of magnesium stearate.

Example 12

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	52.0
Polyvinyl pyrrolidone	7.0
Sodium starch glycolate	5.0
Microcrystalline cellulose	18.8
Alpha-lactose monohydrate	13.0
Magnesium stearate	1.2
Film coating	3.0

Total weight of film-coated tablet: 779 mg

Each of the lapatinib ditosylate monohydrate, microcrystalline cellulose, alpha-lactose monohydrate and sodium starch glycolate are sieved through a Frewitt 1.0 mm sieve. A dry blend of the sieved lapatinib ditosylate monohydrate, the sieved microcrystalline cellulose, the sieved alpha-lactose monohydrate and half of the sieved sodium starch glycolate is filled

into a fluid-bed-granulator (Glatt, GPCG 3/5 granulator). The polyvinyl pyrrolidone is dissolved in purified water (5 parts per weight of water per 1 part per weight of polyvinyl pyrrolidone). Fluid-bed-granulation is started and the polyvinyl pyrrolidone solution is sprayed on top of the dry blend through a 1.0 mm spraying nozzle at 25°C. The wet granules are then further dried in the fluid bed granulator at 35°C. The granules are sieved through a Frewitt 1.0 mm sieve and blended for 10 minutes in a turbula mixer at 25 rpm with the second half of the sieved sodium starch glycolate. Magnesium stearate is added to the resulting blend after having been sieved through a 0.5 mm hand sieve and the blend thus obtained is mixed in a turbula mixer at 25 rpm for 3 minutes. The final blend is compressed into tablets using a Kilian RTS 24 tablet press. The tablets are coated in a Glatt Mini coater (0.8 l drum) using a commercially available Opadry® YS-1-13065-A film coating.

Example 13

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	52.0
Polyvinyl pyrrolidone	7.0
Sodium starch glycolate	5.0
Microcrystalline cellulose	18.8
Alpha-lactose monohydrate	13.0
Calcium stearate	1.2
Film coating	3.0

Total weight of film-coated tablet: 779 mg

The coated tablets are prepared as described in Example 12 with the exception that calcium stearate is used in place of magnesium stearate.

Example 14

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	52.0

HPMC	7.0
Sodium starch glycolate	5.0
Microcrystalline cellulose	18.8
Alpha-lactose monohydrate	13.0
Magnesium stearate	1.2
Film coating	3.0

Total weight of film-coated tablet: 779 mg

The coated tablets are prepared as described in Example 12 with the exception that HPMC is used in place of polyvinyl pyrrolidone.

Example 15

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	52.0
Polyvinyl pyrrolidone	7.0
Croscarmellose sodium	5.0
Microcrystalline cellulose	18.8
Alpha-lactose monohydrate	13.0
Magnesium stearate	1.2
Film coating	3.0

Total weight of film-coated tablet: 779 mg

The coated tablets are prepared as described in Example 12 with the exception that croscarmellose sodium is used in place of sodium starch glycolate.

Example 16

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	52.0

HPMC	7.0
Croscarmellose sodium	5.0
Microcrystalline cellulose	18.8
Alpha-lactose monohydrate	13.0
Magnesium stearate	1.2
Film coating	3.0

Total weight of film-coated tablet: 779 mg

The coated tablets are prepared as described in Example 12 with the exception that HPMC is used in place of polyvinyl pyrrolidone and croscarmellose sodium is used in place of sodium starch glycolate.

Example 17

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	52.0
HPMC	7.0
Croscarmellose sodium	5.0
Microcrystalline cellulose	18.8
Alpha-lactose monohydrate	13.0
Calcium stearate	1.2
Film coating	3.0

Total weight of film-coated tablet: 779 mg

The coated tablets are prepared as described in Example 12 with the exception that HPMC is used in place of polyvinyl pyrrolidone, croscarmellose sodium is used in place of sodium starch glycolate, and calcium stearate is used in place of magnesium stearate.

Example 18

Component	Content in film-coated tablet

	[% by weight]
Lapatinib ditosylate monohydrate	44.0
Polyvinyl pyrrolidone	6.5
Sodium starch glycolate	4.5
Microcrystalline cellulose	25.0
Alpha-lactose monohydrate	16.0
Magnesium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 920 mg

The coated tablets are prepared as described in Example 7 with the exception that the components are used in the amounts as indicated in the above table.

Example 19

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	44.0
Polyvinyl pyrrolidone	6.5
Sodium starch glycolate	4.5
Microcrystalline cellulose	25.0
Alpha-lactose monohydrate	16.0
Calcium arachinate	1.0
Film coating	3.0

Total weight of film-coated tablet: 920 mg

The coated tablets are prepared as described in Example 18 with the exception that calcium arachinate is used in place of magnesium stearate.

Example 20

Component	Content in film-coated tablet

	[% by weight]
Lapatinib ditosylate monohydrate	44.0
HPMC	6.5
Sodium starch glycolate	4.5
Microcrystalline cellulose	25.0
Alpha-lactose monohydrate	16.0
Magnesium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 920 mg

The coated tablets are prepared as described in Example 18 with the exception that HPMC is used in place of polyvinyl pyrrolidone.

Example 21

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	44.0
Polyvinyl pyrrolidone	6.5
Croscarmellose sodium	4.5
Microcrystalline cellulose	25.0
Alpha-lactose monohydrate	16.0
Magnesium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 920 mg

The coated tablets are prepared as described in Example 18 with the exception that croscarmellose sodium is used in place of sodium starch glycolate.

Example 22

Component	Content in film-coated tablet

	[% by weight]
Lapatinib ditosylate monohydrate	44.0
HPMC	6.5
Croscarmellose sodium	4.5
Microcrystalline cellulose	25.0
Alpha-lactose monohydrate	16.0
Magnesium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 920 mg

The coated tablets are prepared as described in Example 18 with the exception that HPMC is used in place of polyvinyl pyrrolidone and croscarmellose sodium is used in place of sodium starch glycolate.

Example 23

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	44.0
HPMC	6.5
Croscarmellose sodium	4.5
Microcrystalline cellulose	25.0
Alpha-lactose monohydrate	16.0
Calcium arachinate	1.0
Film coating	3.0

Total weight of film-coated tablet: 920 mg

The coated tablets are prepared as described in Example 18 with the exception that HPMC is used in place of polyvinyl pyrrolidone, croscarmellose sodium is used in place of sodium starch glycolate, and calcium arachinate is used in place of magnesium stearate.

Example 24

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	40.5
Polyvinyl pyrrolidone	6.2
Sodium starch glycolate	4.3
Microcrystalline cellulose	28.0
Alpha-lactose monohydrate	17.0
Magnesium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 1000 mg

The coated tablets are prepared as described in Example 12 with the exception that the components are used in the amounts as indicated in the above table.

Example 25

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	40.5
Polyvinyl pyrrolidone	6.2
Sodium starch glycolate	4.3
Microcrystalline cellulose	28.0
Alpha-lactose monohydrate	17.0
Calcium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 1000 mg

The coated tablets are prepared as described in Example 24 with the exception that calcium stearate is used in place of magnesium stearate.

Example 26

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	40.5
HPMC	6.2
Sodium starch glycolate	4.3
Microcrystalline cellulose	28.0
Alpha-lactose monohydrate	17.0
Magnesium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 1000 mg

The coated tablets are prepared as described in Example 24 with the exception that HPMC is used in place of polyvinyl pyrrolidone.

Example 27

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	40.5
Polyvinyl pyrrolidone	6.2
Croscarmellose sodium	4.3
Microcrystalline cellulose	28.0
Alpha-lactose monohydrate	17.0
Magnesium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 1000 mg

The coated tablets are prepared as described in Example 24 with the exception that croscarmellose sodium is used in place of sodium starch glycolate.

Example 28

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	40.5
HPMC	6.2
Croscarmellose sodium	4.3
Microcrystalline cellulose	28.0
Alpha-lactose monohydrate	17.0
Magnesium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 1000 mg

The coated tablets are prepared as described in Example 24 with the exception that HPMC is used in place of polyvinyl pyrrolidone and croscarmellose sodium is used in place of sodium starch glycolate.

Example 29

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	40.5
HPMC	6.2
Croscarmellose sodium	4.3
Microcrystalline cellulose	28.0
Alpha-lactose monohydrate	17.0
Calcium stearate	1.0
Film coating	3.0

Total weight of film-coated tablet: 1000 mg

The coated tablets are prepared as described in Example 24 with the exception that HPMC is used in place of polyvinyl pyrrolidone, croscarmellose sodium is used in place of sodium starch glycolate, and calcium stearate is used in place of magnesium stearate.

Example 30

Component	Content in film-coated tablet [% by weight]
Lapatinib ditosylate monohydrate	40.5
HPMC	6.2
Croscarmellose sodium	4.3
Microcrystalline cellulose	28.0
Alpha-lactose monohydrate	17.0
Sodium stearyl fumarate	1.0
Film coating	3.0

Total weight of film-coated tablet: 1000 mg

The coated tablets are prepared as described in Example 24 with the exception that HPMC is used in place of polyvinyl pyrrolidone, croscarmellose sodium is used in place of sodium starch glycolate, and sodium stearyl fumarate is used in place of magnesium stearate.

CLAIMS

1. A pharmaceutical composition comprising an active ingredient, at least one binder, at least one disintegrant, at least one lubricant, and at least one filler, wherein the active ingredient is lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof; and the filler comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition.

2. A pharmaceutical composition according to claim 1, wherein the binder is selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof.

3. A pharmaceutical composition according to claim 1 or 2, wherein the disintegrant is selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof.

4. A pharmaceutical composition according to any of claims 1 to 3, wherein the lubricant is selected from the group consisting of magnesium stearate, calcium stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof.

5. A pharmaceutical composition according to any of claims 1 to 4, wherein the filler comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

6. A pharmaceutical composition according to claim 5, wherein the filler comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight, relative to the weight of

the pharmaceutical composition, of at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

7. A pharmaceutical composition according to any of claims 1 to 6, wherein
the binder is selected from the group consisting of gelatine, polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
the disintegrant is selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
the lubricant is selected from the group consisting of magnesium stearate, calcium stearate, talc, aluminum monostearate, aluminum distearate, aluminum tristearate, zinc stearate, stearic acid, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate, and combinations thereof.

8. A pharmaceutical composition according to claim 7, wherein
the binder is selected from the group consisting of polyvinyl pyrrolidone, polyvinyl acetate, polyvinyl alcohol, hydroxypropylcellulose, hydroxypropylmethylcellulose and combinations thereof;
the disintegrant is selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and combinations thereof;
the lubricant is selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof.

9. A pharmaceutical composition according to claim 8, wherein
the binder is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylmethylcellulose and combinations thereof;
the disintegrant is selected from the group consisting of sodium starch glycolate, croscarmellose sodium and combinations thereof;
the lubricant is selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
the filler comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and 10 to 20% by weight,

relative to the weight of the pharmaceutical composition, of at least one further compound selected from the group consisting of mannitol, calcium hydrogen phosphate, lactose and starch.

10. A pharmaceutical composition according to claim 9, wherein
the binder is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylmethylcellulose and combinations thereof;
the disintegrant is selected from the group consisting of sodium starch glycolate, croscarmellose sodium and combinations thereof;
the lubricant is selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
the filler comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and lactose in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

11. A pharmaceutical composition according to claim 10 comprising
30 to 60% by weight, relative to the weight of the pharmaceutical composition, of lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof;
1 to 20% by weight, relative to the weight of the pharmaceutical composition, of a binder selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylmethylcellulose and combinations thereof;
0.5 to 8% by weight, relative to the weight of the pharmaceutical composition, of a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium and combinations thereof;
0.01 to 3% by weight, relative to the weight of the pharmaceutical composition, of a lubricant selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, magnesium behenate, calcium behenate, magnesium arachinate, calcium arachinate and combinations thereof;
a filler which comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the weight of the pharmaceutical composition, and lactose in an amount of 10 to 20% by weight, relative to the weight of the pharmaceutical composition.

12. A pharmaceutical composition according to any of claims 1 to 11 wherein the microcrystalline cellulose has a median particle size of 50 to 100 µm.

13. A pharmaceutical composition according to any of claims 1 to 12 which is a tablet or a coated tablet.

14. Process for producing the pharmaceutical composition according to any of claims 1 to 13 comprising
    (a) granulating a mixture comprising lapatinib or a pharmaceutically acceptable salt or solvate or solvated salt thereof, the filler, and optionally the disintegrant, using an aqueous solution of the binder as granulation liquid;
    (b) drying the granules obtained in step (a);
    (c) mixing the dried granules with the lubricant, and optionally the disintegrant;
    provided that the disintegrant is added in step (a) and/or (c).

15. Process according to claim 14 wherein the granules are dried to a water content of 0.5 to 3% by weight.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/053087

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K9/28
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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/113649 A1 (SMITHKLINE BEECHAM CORK LTD [IE]; CARTER BARRY HOWARD [US]; CAMPBELL D) 26 October 2006 (2006-10-26) cited in the application formula II page 18, line 26 - page 19, line 11 -----	1-15
X	WO 2010/099150 A1 (SMITHKLINE BEECHAM CORK LTD [IE]; CARTER BARRY HOWARD [US]; SUEDA KATS) 2 September 2010 (2010-09-02) examples; tables 7-9 -----	1-15
X	EP 2 158 912 A1 (RATIOPHARM GMBH [DE]) 3 March 2010 (2010-03-03) abstract paragraphs [0025], [0026] paragraphs [0028] - [0039] -----	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
20 May 2014	30/05/2014

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/053087

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