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BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

- *as to the identity of the inventor (Rule 4.17(i))*
- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- *of inventorship (Rule 4.17(iv))*

Published:

- *with international search report (Art. 21(3))*

(54) **Title:** STABLE PHARMACEUTICAL COMPOSITION OF AFATINIB

(57) **Abstract:** A solid oral dosage form comprising therapeutically effective amount of afatinib or a salt thereof and an acid in an amount sufficient to provide an acidic microenvironment of pH less than 3.5, wherein the solid dosage form is a dry solid dosage form and wherein when the solid oral dosage form is stored at condition of 40°C and 75% relative humidity for three months, the total impurities in the solid oral dosage form do not increase to more than 2.5% by weight of afatinib.



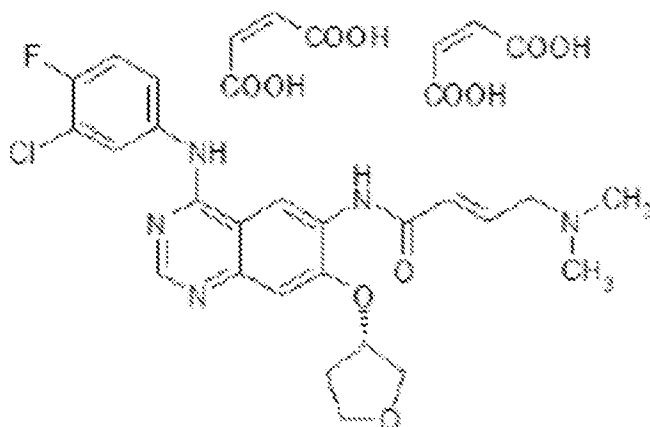
STABLE PHARMACEUTICAL COMPOSITION OF AFATINIB

FIELD OF INVENTION

A solid oral dosage form comprising therapeutically effective amount of afatinib or a salt thereof and an acid in an amount sufficient to provide an acidic microenvironment of pH less than 3.5, wherein the solid dosage form is a dry solid dosage form.

BACKGROUND OF THE INVENTION

Afatinib is a synthetic quinazoline derivative. It has one chiral centre; the drug is the pure 3S enantiomer. It is available in the form of a salt formed with maleic acid. It has two basic groups, the dimethylamine (pKa 8.2) and the quinazoline (pKa 5.0). It is also referred to as BIBW 2992. It is commercially available under the brand name of GILOTRIF® tablets which contain afatinib, as the dimaleate salt. The chemical structure is depicted below:



These GILOTRIF® tablets for oral administration are available in 40 mg, 30 mg, or 20 mg of afatinib (equivalent to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate, respectively).

Afatinib dimaleate is susceptible to moisture affecting its chemical stability and leading to decrease of the active principle and increase of contamination with hydrolytic degradation products. The present inventors have found a stable solid oral dosage form of afatinib.

SUMMARY OF THE INVENTION

A solid oral dosage form comprising therapeutically effective amount of afatinib or a salt thereof and an acid in an amount sufficient to provide an acidic microenvironment of pH less than 3.5, wherein the solid dosage form is a dry solid dosage form and wherein when the solid oral dosage form is stored at condition of 40⁰C and 75% relative humidity for three months, the total impurities in the solid oral dosage form do not increase to more than 2.5% by weight of afatinib.

The present invention also provides a process for the preparation of a solid oral dosage comprising:

- a. granulating pharmaceutically acceptable excipients and an acid with water and drying the granules at 105⁰C until the loss on drying is between 0.5-2.5% w/w,
- b. dry blending the granules of step 'a' with afatinib or its pharmaceutically acceptable salt, an acid in an amount sufficient to provide an acidic microenvironment, pharmaceutically acceptable excipients and lubricants,
- c. converting the dry blend of step 'b' into a solid dosage form.

DETAILED DESCRIPTION OF THE INVENTION

The term 'provides an acidic microenvironment' is understood by the following test: the solid oral dosage form in the form of a unit dosage form is taken and dispersed in 30 ml of purified water. The pH of the dispersion is measured. The term 'acidic microenvironment' is intended to mean a pH obtained by the above test is equal to or less than 3.5, preferably, 1.5 to 3.

The total impurities in the solid oral dosage form arising from afatinib include known and unknown impurities. The known impurities includes,

1) *Pyrrolidone Degradation Impurity*: 1-{4-[(3-chloro-4-fluorophenyl)amino]-7-[(3S)-tetrahydrofuran-3-yloxy]quinazolin-6-yl}-5-hydroxypyrrolidin-2-one;

2) *Nitro Oxy THF CFA derivative*: 6-Nitro-4-[(3-chloro-4-fluorophenyl)amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline;

3) *Amino oxy THF CFA derivative*: 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline.

4) Other unknown impurities are nomenclature based on the relative retention time, since these impurities are not characterized. One such impurity is detected at 0.96. The highest unknown
5 impurities are detected at relative retention time such as at 0.01, 0.011, 0.08, 0.09, 0.45, 0.47, and 0.86.

The solid oral dosage form of the present invention, comprises therapeutically effective amount of afatinib or a salt thereof and an acid in an amount sufficient to provide an acidic microenvironment of pH less than 3.5, wherein the solid dosage form is a dry solid dosage form
10 and wherein when the solid oral dosage form is stored at condition of 40°C and 75% relative humidity for three months, the total impurities in the solid oral dosage form do not increase to more than 2.5% by weight of afatinib.

According to the present invention, afatinib may be present as its free base or as its salt. In one preferred embodiment, afatinib is present in the form of a dimaleate salt. It may be present in
15 amounts of 20 mg, 30 mg, or 40 mg of afatinib (equivalent to 29.56 mg, 44.34 mg, or 59.12 mg afatinib dimaleate, respectively). However, it is possible to include other suitable amounts of afatinib in the solid oral dosage form. When afatinib is present as a free base in the solid oral dosage form, the acid providing an acidic microenvironment is present in amounts enough to create an acidic microenvironment as defined herein. In another embodiment, the afatinib may be
20 present as its pharmaceutically acceptable salt and further comprise an acid in an amount sufficient to provide the acidic microenvironment as defined herein. In a preferred embodiment, afatinib or its pharmaceutically acceptable salt is a sole active ingredient.

The acid that provides an acidic microenvironment can be any acid capable of donating its
25 protons in the microenvironment. Without wishing to be bound by any theory, it is believed that the solid oral dosage form of the present invention arrests degradation of afatinib or its pharmaceutically acceptable salt which otherwise degrades rapidly and generates a large amount of total impurities which are calculated with respect to the afatinib free base present in the solid oral dosage form. More preferably, the acid is an organic acid. It is understood by person of skill

in the art that the at least one acid is not a long chain fatty acid such as stearic acid because such acid being hydrophobic is incapable of providing an acidic microenvironment. Suitable acids include, but are not particularly limited to, acetic acid, ascorbic acid, nitric acid, aspartic acid, sulfonic acid, sulfuric acid, maleic acid, glutamic acid, formic acid, succinic acid, phosphoric acid, tartaric acid, hydrobromic acid, propionic acid, benzenesulfonic acid, lactic acid, bicarbonic acid, bitartaric acid, oxalic acid, butyric acid, calcium edentate acid, carbonic acid, citric acid, edetic acid, toluenesulfonic acid, edisylic acid, fumaric acid, gluconic acid, methylnitric acid, hydrochloric acid, hydroiodic acid, isethionic acid, lactobionic acid, mandelic acid, pantothenic acid, monohydrogen phosphoric acid, dihydrogen phosphoric acid, sulfamic acid, methanesulfonic acid, malic acid, naphthalenesulfonic acid, galacturonic acid and the like. In certain embodiment, the acid used is in amounts in the range from 0.1 % to 20 % by weight of the unit solid oral dosage form, preferably, the amount of acid is 1,2,3,4,5,6,7,8,9,10,11,12,13,14 or 15 % by weight of the solid oral dosage form. The acid may or may not be present in close vicinity to afatinib. When present in close vicinity, for e.g., both the acid and afatinib together may be present in the form of granules or powder, which may be converted into a granule filled into capsule, sachet, pouch or compressed into a tablet. Alternatively, the powder blend of acid and afatinib may be filled into sachet, pouch, capsule or compressed into a tablet, mini-tablet. When the acid is not in close vicinity to the afatinib, it may be present either in granular phase and afatinib in the extragranular phase, or vice versa or in both. In such one embodiment, the acid may be present in the outer coating which is not in close contact with afatinib.

Other suitable pharmaceutically acceptable excipients include, but are not limited to, diluents such as mannitol, dextrose, lactose, lactose anhydrous, microcrystalline cellulose, starch, pregelatinized starch, lactitol, preferably anhydrous grades of such excipients are preferred. The solid oral dosage form may further, include, disintegrants, such as croscarmellose sodium, crospovidone, sodium starch glycolate, polacrillin potassium, pregelatinized starch and the like and mixtures thereof. Other categories of excipients such as lubricants, glidants may be included in the solid oral dosage form of the present invention.

The solid oral dosage form according to the present invention may be in the form of a powder, granules, compacts which may be either filled into hard gelatin capsule or compressed into tablets. According to the present invention, the solid oral dosage form is a dry solid dosage form which means that it has initial moisture content less than 4.0% by weight of the solid oral dosage form. It is preferably less than about 2.5% by weight of the unit dosage form, more preferably less than about 1% by weight of the solid oral dosage form. The moisture content in a solid dosage form may be determined by any methods known in the art; preferably it may be determined by Karl Fischer method. The solid oral dosage form is packed in a container together with a moisture resistant means such as desiccant. The moisture resistant means include, but are not limited to, bottle/container made up of moisture resistant polymeric materials like high density polyethylene, high density polypropylene and the like. Additionally, the ingress of the moisture may be prevented by use of a desiccant such as activated alumina, calcium sulfate, calcium chloride, bentonite clay, molecular sieves, silica bags, silica pouches or the like.

The solid oral dosage form of the present invention may be prepared by wet aqueous granulation, dry granulation, direct compression and other conventional methods known in the art for preparation of granules, pellets, tablets or capsules. Preferably, however afatinib is not contacted with water. In certain embodiments, contact with water is avoided for e.g. in dry methods such as dry granulation methods and direct compression methods. In one embodiment, wet granulation method can be also used where the granulating fluid is non-aqueous. In another embodiment, a part of the pharmaceutical excipients is wet granulated with aqueous fluid and then dried. Separately a blend of afatinib or its pharmaceutically acceptable salt with another part of pharmaceutical excipients preferably including the acid that provides an acidic microenvironment is prepared and then blended with the dried granules to avoid contact with water. The acid that provides an acidic microenvironment be present in the granular phase or the blend or both.

One process of preparation of a solid oral dosage form of the present invention comprises:

- a. granulating pharmaceutically acceptable excipients with water and drying the granules at 105°C until loss on drying is between 0.5-2.5% by weight,

- b. dry blending the granules of step 'a' with afatinib or its pharmaceutically acceptable salt, an acid in amount sufficient to provide an acidic microenvironment, pharmaceutically acceptable excipients and lubricants, and
- c. converting the dry blend of step 'b' into a solid oral dosage form.

5 Another process of preparation of a solid oral dosage form comprises:

- a. granulating pharmaceutically acceptable excipients and an acid in amount sufficient to provide an acidic microenvironment with water and drying the granules at 105⁰C until loss on drying is between 0.5-2.5% by weight,
- b. dry blending the granules of step 'a' with afatinib or its pharmaceutically acceptable salt,
10 pharmaceutically acceptable excipients and lubricants, and
- c. converting the dry blend of step 'b' into a solid oral dosage form.

Yet another process of preparation of a solid oral dosage form comprises:

- a. granulating pharmaceutically acceptable excipients and an acid with water and drying the granules at 105⁰C until loss on drying is between 0.5-2.5% by weight,
- 15 b. dry blending the granules of step 'a' with afatinib or its pharmaceutically acceptable salt, an acid in amount sufficient to provide an acidic microenvironment, pharmaceutically acceptable excipients and lubricants, and
- c. converting the dry blend of step 'b' into a solid oral dosage form.

Still another process of preparation of a solid oral dosage form comprises:

- 20 a. blending the pharmaceutically acceptable excipients with an acid in an amount sufficient to provide an microenvironment and afatinib or its pharmaceutically acceptable salt and drying the blend at 105⁰C until loss on drying is between 0.5-2.5% by weight,
- b. dry blending the blend of 'a' with disintegrants and lubricants, and
- c. converting the dry blend of step 'c' into a solid oral dosage form.

- 25 The total impurities and/or the known and unknown impurities *i.e.* the stability and the degree of stabilization of the solid oral dosage form such as capsules or tablets is measured by storing it in closed containers at 40⁰C and 75% relative humidity for three months and quantifying the impurities. The solid oral dosage form is said to be stable when its total impurities do not increase to more than 2.5% by weight of afatinib, preferably to not more than 1.5% and more

preferably to not more than 0.5%. The total impurities increase by not more than 1.5% from the initial value, preferably by not more than 0.75 % and more preferably by not more than 0.5%. In highly preferred embodiments, the total impurities increase by not more than 0.25%. In contrast, a solid oral dosage form without the acid that provides acidic microenvironment, under the same test, has high increase in levels of total impurities for instance as high as about 4% by weight of afatinib content present in the solid oral dosage form. In preferred embodiment, the pyrrolidone degradation impurity does not increase to more than 1.2% by weight of afatinib, preferably to not more than 0.75% and more preferably to not more than 0.5% w/w, when the solid oral dosage form is stored at 40°C and 75% relative humidity for three months.

Hereinafter, the invention will be more specifically described with reference to examples. The examples are not intended to limit the scope of the invention and are merely used as illustrations.

Table 1: COMPARATIVE EXAMPLE (without any acid)

Category	Ingredients	% by weight
Active Ingredient	Afatinib dimaleate	16.1
Diluent	Lactose anhydrous	52.6
	Microcrystalline cellulose	13.6
Disintegrant	Crospovidone	9.5
Lubricant	Colloidal silicon dioxide	4.1
	Magnesium stearate	1.2
Film coating	Hydroxypropyl methylcellulose	2.9

The comparative example was prepared by co-shifting lactose anhydrous, microcrystalline cellulose, crospovidone, and colloidal silicon dioxide through 40# sieve and blending them with specified amount of afatinib dimaleate. The blend was mixed with magnesium stearate passed through 60# sieve. The lubricated blend was compressed into tablets. The compressed tablet cores were coated with hydroxypropyl methyl cellulose based film coating. The moisture content in the coated tablet was 2.8%. The pH of the solution of the coated tablet of comparative example dispersed in 30 ml of purified water was 3.5. The coated tablets of comparative example were stored under accelerated stability condition (40°C and 75% relative humidity) in closed containers, along with desiccant and were subjected to chemical analysis. The stability report of the analysis is given below in Table 2.

Table 2: Accelerated stability data for comparative example stored at 40°C and 75% RH

Impurities	Comparative example		
	Initial	One month	Three months
Pyrrolidone degradation impurity	0.063 %	0.515 %	2.913 %
Total impurities	0.239 %	0.762 %	4.056 %

It was found that the pyrrolidone degradation impurity and total impurities levels significantly increased when stored at 40°C and 75% relative humidity for one and three months. Hence, the conventional formulations were found to be unstable.

EXAMPLE I

Table 3: Composition details

Category	Ingredients	% by weight
Active Ingredient	Afatinib Dimaleate	15.8
Diluent	Lactose Anhydrous	45.2
	Microcrystalline Cellulose	13.4
Acid	Tartaric Acid	9.4
Disintegrant	Crospovidone	9.4
Lubricant	Colloidal Silicon Dioxide	2.7
	Magnesium Stearate	1.2
Film coating	Hydroxypropyl methylcellulose	2.9

Preparation of dry granules containing an acid:

A part of lactose anhydrous, microcrystalline cellulose and a part of crospovidone were co-sifted and was granulated using tartaric acid aqueous solution. The granules were dried until the loss on drying was less than 2.5%. The dried granules were passed through 40 # sieve.

Mixing afatinib with dry granules, lubrication and compression:

The milled granules were blended with the specified amount of afatinib dimaleate, the remaining parts of lactose anhydrous and crospovidone. The blend was mixed with colloidal silicon dioxide and magnesium stearate. The lubricated blend was compressed into tablets. The compressed tablet cores were coated with hydroxypropyl methyl cellulose based film coating and packed in a container together with a desiccant. The moisture content in the coated tablet was 2%. The pH of the solution of the coated tablet dispersed in 30 ml of purified water was 2.15. The coated tablets

were stored under accelerated stability condition (40°C and 75% relative humidity) in closed containers, along with desiccant and were subjected to chemical analysis.

Table 4: Accelerated stability data for Tablets of example I stored at 40°C and 75% RH

Impurities	Initial	Three months
Pyrrolidone degradation impurity	0.123%	0.392%
Total impurities	0.412%	1.502%

- 5 It was found that the total impurities did not increase by more than 1.1% from the initial value as compared to increased total impurity levels of 3.8% from initial value in a comparative solid oral dosage form not containing acid(s) which provide an acid microenvironment of pH less than 3.5.

EXAMPLE II

Table 5: Composition details

Category	Ingredients	% by weight
Active Ingredient	Afatinib Dimaleate	15.9
Diluent	Lactose Anhydrous	44.7
	Microcrystalline Cellulose	13.5
Acid	Tartaric Acid	4.1
	Ascorbic Acid	6.7
Disintegrant	Crospovidone	8.1
Lubricant	Colloidal Silicon Dioxide	2.7
	Magnesium Stearate	1.4
Film coating	Hydroxypropyl methylcellulose	2.9

10

Preparation of dry granules containing an acid:

A part of lactose anhydrous, microcrystalline cellulose and a part of crospovidone were co-sifted and was granulated using tartaric acid aqueous solution. The granules containing tartaric acid were dried until the loss on drying was less than 2.5% and passed through 40 # sieve.

15 Mixing afatinib with dry granules, additional acid, lubrication and compression:

The milled granules were blended with the specified amount of afatinib dimaleate, remaining part of lactose anhydrous and ascorbic acid. The blend was mixed with colloidal silicon dioxide and magnesium stearate. The lubricated blend was compressed into tablets. The compressed tablet cores were coated with hydroxypropyl methyl cellulose based film coating and packed in a
20 container together with a desiccant. The moisture content in the coated tablet was 1.8%. The pH

of the solution of the coated tablet dispersed in 30 ml of purified water was 2.58. The coated tablets were stored under accelerated stability condition (40°C and 75% relative humidity) in closed containers, along with desiccant and were subjected to chemical analysis.

Table 6: Accelerated stability data for Tablets of Example II stored at 40°C and 75% RH

Impurities	Initial	Three months
Pyrrolidone degradation impurity	0.07%	0.379%
Total impurities	0.503%	1.204%

It was found that the total impurities did not increase by more than 0.75% from the initial value as compared to increased total impurity levels of 3.8% from initial value in a comparative solid oral dosage form not containing acid(s) which provide an acid microenvironment of pH less than 3.5.

EXAMPLE III and IV

Table 7: Composition details

Category	Ingredients	% by weight	
		Example III	Example IV
Active Ingredient	Afatinib Dimaleate	15.9	15.9
Diluent	Lactose Anhydrous	50.1	46.1
	Microcrystalline Cellulose	13.5	13.5
Acid	Tartaric Acid	-	4.0
	Citric Acid	4.0	4.0
Disintegrant	Crospovidone	8.1	8.1
Lubricant	Colloidal Silicon Dioxide	4.1	4.1
	Magnesium Stearate	1.4	1.4
Film coating	Hydroxypropyl methylcellulose	2.9	2.9

Lactose anhydrous, microcrystalline cellulose and crospovidone were co-sifted through 40 # sieve and blended with specified amount of afatinib dimaleate and acid. The blend was mixed with colloidal silicon dioxide and magnesium stearate. The lubricated blend was compressed into tablets. The compressed tablet cores were coated with hydroxypropyl methyl cellulose based film coating and packed in a container together with a desiccant. The moisture content in the tablets of Example II and IV were 2.7% and 2.8%, respectively. The pH of the solution of the coated tablet of example III and IV dispersed in 30 ml of purified water was 2.55 and 2.48, respectively. The coated tablets of example III and IV were stored under accelerated stability

condition (40⁰C and 75% relative humidity) in closed containers, along with desiccant and were subjected to chemical analysis. The stability report of example III and IV are given below in Table 8 and Table 9 respectively.

Table 8: Accelerated stability data for Tablets of example III stored at 40⁰C and 75% RH

Impurities	Initial	14 Day
Pyrrolidone degradation impurity	0.049	0.099
Total impurities	0.281	0.343

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Table 9: Accelerated stability data for Tablets of example IV stored at 40⁰C and 75% RH

Impurities	Initial	14 Day
Pyrrolidone degradation impurity	0.052	0.098
Total impurities	0.263	0.355

We claim:

1. A solid oral dosage form comprising therapeutically effective amount of afatinib or a salt thereof and an acid in an amount sufficient to provide an acidic microenvironment of pH less than 3.5, wherein the solid dosage form is a dry solid dosage form and wherein when
5 the solid oral dosage form is stored at condition of 40⁰C and 75% relative humidity for three months, the total impurities in the solid oral dosage form do not increase to more than 2.5% by weight of afatinib.
2. A solid oral dosage form as in claim 1, wherein the acid is tartaric acid and/or citric acid.
3. A solid oral dosage form as in claim 2, wherein the acid further comprises of ascorbic
10 acid.
4. A solid oral dosage form as in claim 1, wherein when the solid oral dosage form is stored at condition of 40⁰C and 75% relative humidity for three months, the pyrrolidone degradation impurity in the solid oral dosage form does not increase to more than 0.5% by weight of afatinib.
- 15 5. A process for the preparation of a solid oral dosage form comprising:
 - a. granulating pharmaceutically acceptable excipients and an acid with water and drying the granules at 105⁰C until loss on drying is between 0.5-2.5% w/w,
 - b. dry blending the granules of step 'a' with afatinib or its pharmaceutically acceptable salt, an acid in amount sufficient to provide an acidic
20 microenvironment, pharmaceutically acceptable excipients and lubricants, and
 - c. converting the dry blend of step 'b' into a solid dosage form.

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2017/050066

A. CLASSIFICATION OF SUBJECT MATTER IPC: A61K 31/517 (2006.01); A61K 47/12 (2006.01) 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) TXTE, TXTG, wpi		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0078735 A1 (BOEHRINGER INGELHEIM PHARMA KG, HIMMELSBACH, FRANK, LANGKOPF, ELKE, METZ, THOMAS, SOLCA, FLAVIO, JUNG, BIRGIT, BAUM, ANKE) 28 December 2000 (28.12.2000) page 39, 2nd paragraph; claim 1	1-2
A	WO 0250043 A1 (BOEHRINGER INGELHEIM PHARMA KG, HIMMELSBACH, FRANK, LANGKOPF, ELKE, BLECH, STEFAN, JUNG, BIRGIT, BAUM, ELKE, SOLCA, FLAVIO) 27 June 2002 (27.06.2002) page 20, 3rd paragraph; claim 1	1-5
A	WO 2005011701 A1 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH, BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, JUNG, BIRGIT, PUESCHNER, HUBERT) 10 February 2005 (10.02.2005) page 4, last paragraph-page 5, 1st paragraph; page 7, 3rd paragraph-page 8, 1st paragraph; claims	1-5
☐ 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 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "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 22 May 2017 (22.05.2017)		Date of mailing of the international search report 23 May 2017 (23.05.2017)
Name and mailing address of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24-535		Authorized officer KRENN M. Telephone No. +43 / 1 / 534 24-435

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2017/050066

Box No. II		Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: 1. ☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: 2. ☒ Claims Nos.: 4 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically: The characterization of a composition by stability parameters is inappropriate. A composition should be described by those components causing said stability. 3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).		
Box No. III		Observations where unity of invention is lacking (Continuation of item 3 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows: 1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. 2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees. 3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee. ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation. ☐ No protest accompanied the payment of additional search fees.		

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