IN THE UNITED STATED PATENT AND TRADEMARK OFFICE

Applicant : SATHE ET AL. Group Art Unit: 1611

Appln. No. : 16/477,661 Examiner: BARBARA FRAZIER

Filing Date : July 12, 2019 Confirmation No.: 9756

Attorney Docket No.: SATH3002/TL

Title: Pharmaceutical composition of apixaban

AMENDMENT AND REPLY UNDER 37 CFR 1.111

MS Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Dear Honorable Commissioner,

This communication is responsive to the Non-Final office Action dated October 29, 2020 concerning the above-referenced patent application. No extension of time is necessary because this response is being filed by the due date of January 29, 2021.

Amendments to the Claims are reflected in the listing of claims which begin on page 2 of this document.

Remarks begin on page 7 of this document.

AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims

1. (Original) A pharmaceutical composition comprising apixaban having a D_{90} particle size of more than 100 microns, a diluent, a surfactant, a disintegrant and a lubricant.

2. (Original) The pharmaceutical composition according to claim 1, wherein the D_{90} particle size of the apixaban is between 300 and 1000 microns.

3. (Original) The pharmaceutical composition according to claim 1, wherein the D_{90} particle size of the apixaban is between 350 and 800 microns.

4. (Original) The pharmaceutical composition according to claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of a binder, a glidant, a coating agent, a plasticizer, a coloring agent, and a viscosity enhancer.

5. (Previously Cancelled)

6. (Original) The pharmaceutical composition according to claim 1, wherein the composition further comprises a binder.

7. (Original) The pharmaceutical composition according to claim 1, wherein the composition is in a dosage form selected from the group consisting of tablet, capsule, powder, caplet, granules, pellets, tablet in tablet, tablet in capsule, pellets in capsule, powder in capsule, and granules in capsule.

8. (Original) The pharmaceutical composition according to claim 1, wherein the composition is a tablet.

9. (Currently Amended) The pharmaceutical composition according to claim 1, wherein the diluent is selected from the group consisting of microcrystalline cellulose, microfine cellulose, powdered cellulose, lactose, dibasic calcium phosphate, tribasic calcium phosphate, starch, pre-gelatinized starch, calcium carbonate, calcium sulfate, magnesium carbonate, magnesium oxide, dextrates, dextrin, dextrose, kaolin, maltodextrin, mannitol, sucrose, methyl dextrin, sorbitol, and a combination thereof.

10. (Original) The pharmaceutical composition according to any one of claims 4 and 6, wherein binder is selected from the group consisting of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxy methyl cellulose, methyl cellulose, ethyl cellulose, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohols, pregelatinized starch, starch paste, sucrose, glucose, acacia, tragacanth, gelatin, alginic acid, sodium alginate, and a combination thereof.

11. (Original) The pharmaceutical composition according to claim 1, wherein the surfactant is selected from the group consisting of self-emulsifying glyceryl monooleate, docusate sodium, emulsifying wax BP, sodium lauryl sulfate (SLS), benzethonium chloride, cetrimide, cetylpyridinium chloride, lauric acid, myristyl alcohol, sorbic acid, emulsifying wax, glyceryl monooleate, phospholipids, polyoxyethylene alkyl ethers (macrogol cetostearyl ether, macrogol lauryl ether, macrogol oleyl ether, macrogol stearyl ether), polyoxyethylene castor oil derivatives (macrogolglycerol ricinoleate, macrogolglycerol hydroxystearate), polyoxyethylene sorbitan fatty acid esters (polysorbate 20, 40, 60, and 80), polyoxyethylene stearates, polyoxylglycerides (caprylocaproyl polyoxylglycerides, lauroyl polyoxylglycerides, linoleoyl polyoxylglycerides, oleoyl polyoxylglycerides and stearoyl polyoxylglycerides), sorbitan esters (sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan sesquioleate, sorbitan stearate, sorbitan trioleate), triethyl citrate, and a combination thereof.

12. (Original) The pharmaceutical composition according to claim 1, wherein the disintegrant is selected form the group consisting of carboxymethylcellulose calcium, carboxymethylcellulose sodium, croscarmellose sodium, crospovidone, polacrilin potassium, sodium alginate, sodium starch glycolate, and a combination thereof.

13. (Original) The pharmaceutical composition according to any one of claims 4 to 6, wherein the lubricant is selected from the group consisting of magnesium stearate, aluminium stearate, sucrose stearate, calcium stearate stearic acid, talc, fumaric acid, palmitic acid, sodium stearyl fumarate, glyceryl monostearate, carnauba wax, hydrogenated vegetable oils, mineral oil, polyethylene glycols, and a combination thereof.

14. (Previously Cancelled)

15. (Previously Cancelled)

16. (Previously Withdrawn) A process for preparing a tablet comprising apixaban, the process comprises the steps of:

co-sifting a diluent and a disintegrant through a sieve to prepare a dry mix;

dissolving apixaban having a D90 particle size of more than 100 microns in an organic solvent to prepare a drug solution;

spraying the drug solution onto the dry mix in a fluidized bed processor to produce drug granules;

drying the drug granules in a fluidized bed processor to produce dried drug granules;

spraying a solution of a surfactant onto the dried drug granules to produce surfactant coated drug granules;

drying the surfactant coated drug granules in a fluidized bed processor to prepare dried surfactant coated drug granules;

sifting the dried surfactant coated drug granules through a sieve to produce sifted granules;

pre-lubricating the sifted granules to produce an extragranular pre-lubricated blend;

lubricating the extragranular pre-lubricated blend with a lubricant to produce a lubricated blend; and

compressing the lubricated blend to produce an uncoated tablet; and

optionally coating the uncoated tablet.

17. (Previously Withdrawn) The process according to claim 16, wherein the diluent is a mixture of microcrystalline cellulose and anhydrous lactose, the disintegrant is croscarmellose sodium, the surfactant is sodium lauryl sulphate, and the lubricant is magnesium stearate.

18. (Previously Withdrawn) A process for preparing a tablet comprising apixaban, the process comprises the steps of:

co-sifting a diluent and a disintegrant through a sieve to prepare a dry mix;

mixing a surfactant, a binder and a purified water to produce a binder solution; dispersing apixaban having a D_{90} particle size of more than 100 microns in the binder solution to produce a drug solution;

spraying the drug solution onto the dry mix in a rapid mixer granulator to produce drug granules;

drying the drug granules in a rapid dryer to produce dried drug granules;

sifting the dried drug granules through a sieve to produce sifted granules; pre-lubricating the sifted granules to produce pre-lubricated granules;

lubricating the pre-lubricated granules with a lubricant to produce a lubricated blend; compressing the lubricated blend to produce an uncoated tablet; and

optionally coating the uncoated tablet.

19. (Previously Withdrawn) The process according to claim 16, wherein the diluent is a mixture of microcrystalline cellulose and anhydrous lactose, the disintegrant is croscarmellose sodium, the surfactant is sodium lauryl sulphate, the binder is polyvinylpyrrolidone, and the lubricant is magnesium stearate.

20. (Previously Withdrawn) The process according to any one of claims 16 and 18, wherein the D90 particle size of the apixaban is between 300 and 1000 microns.

21. (Currently Amended) The pharmaceutical composition according to claim 1, comprising:

a) apixaban having a D_{90} particle size of more than 100 microns;

b) a diluent selected from the group consisting of microcrystalline cellulose, anhydrous lactose and a combination thereof;

c) a disintegrant which is croscarmellose sodium;

d) a surfactant which is sodium lauryl sulphate; and

e) a lubricant which is magnesium stearate;

wherein said diluent is a mixture of microcrystalline cellulose and lactose.

22: (Currently Amended) The pharmaceutical composition according to claim 1, wherein the composition is prepared in a tablet form by :

co-sifting a diluent and a disintegrant through a sieve to prepare a dry mix;

dissolving apixaban having a D_{90} particle size of more than 100 microns in an organic solvent to prepare a drug solution;

spraying the drug solution onto the dry mix in a fluidized bed processor to produce drug granules;

drying the drug granules in a fluidized bed processor to produce dried drug granules; spraying a solution of a surfactant onto the dried drug granules to produce surfactant coated drug granules;

drying the surfactant coated drug granules in a fluidized bed processor to prepare dried surfactant coated drug granules;

sifting the dried surfactant coated drug granules through a sieve to produce sifted granules;

pre-lubricating the sifted granules to produce an extragranular pre-lubricated blend;

lubricating the extragranular pre-lubricated blend with a lubricant to produce a lubricated blend; and

compressing the lubricated blend to produce an uncoated tablet; and

optionally coating the uncoated tablet.

REMARKS

I. Status of the Application

Claims 1-4, 6-13 and 16-22 are pending in this application. Claims 16-20 stand withdrawn from consideration as being directed to a non-elected subject matter. Claims 1-4, 6-13, 21 and 22 stand rejected based on prior art ground. Claim 9 is amended to address a minor typographical error. Claims 21 and 22 are amended as shown herein. Support for the claim amendments can be found throughout the Applicant's specification as originally filed. The amendments do not go beyond the scope of the application as filed as new matter is not added to the application. No claim has been added or cancelled with this amendment.

In view of the following discussion, the Examiner is respectfully requested to reconsider and withdraw the objections and rejections.

II. Response to 35 U.S.C. § 112 (b) Rejections

The Office Action rejects claims 21 and 22 under 35 U.S.C. 112(b) or 35 U.S.C. 112(pre-AIA) second paragraph as being indefinite.

Claims 21 and 22 have been amended. Applicants believe that these amendments should obviate the rejections and therefore request that they be withdrawn.

III. Response to Claim Objections

The Office Action objects to claim 22 because of informalities.

Claim 22 has been amended per the suggestion of the Examiner. Withdrawal of the objection is respectfully requested.

IV. Response to 35 U.S.C. § 103 Rejections

The Office Action rejects claims 1-4, 6-13, 21 and 22 under 35 U.S.C. 103 as allegedly being unpatentable over Meergans et al. (US 2015/0272891) hereinafter referred to as "**Meergans**" in view of Stanic Ljubin et al. (WO 2015/121472) hereinafter referred to as "**Stanic**".

After careful consideration of the rejection and of the Patent Office's comments applicants respectfully traverse the rejection and offer the following remarks.

The present invention provides a pharmaceutical composition comprising apixaban particles having a D90 more than 100 μm, which provides desired oral bioavailability equivalent to the reference listed drug product 'ELIQUIS®'. The adequate drug bioavailability provided by the use of the apixaban particles with a D90 of more than 100 μm was both surprising and unexpected.

It is generally known in the art that particle size reduction improves dissolution rate of therapeutically active compounds and that larger drug particles do not dissolve sufficiently rapidly to give desired dissolution profiles and/or bioavailability. Previous to the present invention when providing apixaban formulations, the successful trend consisted in using apixaban particles having a D90 less than about 89 μm. The US Patent No. 9,326,945 to Bristol Myers Squibb Co. (hereinafter 'US9326945') was a good example illustrating the aforementioned trend of the prior art. US9326945 pointed out the importance of the particle size of apixaban particles to be used in dosage forms, and put strong emphasis on the requirement that apixaban particles should have a D90 equal to or less than about 89 μm in order to facilitate consistent in-vivo drug dissolution in human at physiologic pH and to meet bioequivalence criteria. See, US9326945, abstract, column 1, lines 56-60, and column 9, lines 30-33. Said teachings formed a prejudice that for the achievement of consistent human in-vivo dissolution it was essential to use smaller particles of apixaban (D90 less than 89 μm). The inventors of the present application have explicitly made reference to this prior art as disclosed in US9326945 in paragraph [0006] of the present application. In view of the established trend in the prior art represented by US9326945 one of ordinary skill in the art would be prejudiced from using apixaban particles having a D90 more than about 89 μm. Acting against such a prejudice or trend, as in the present case, may be considered to indicate the existence of inventive step.

Meergans discloses oral dosage forms for modified release of apixaban. Although Meergans mentions in paragraph [0024] that the D90 particle size distribution for apixaban present in the dosage form is 90 μm or greater, in particular from 95 to 500 μm, it only exemplifies dosage forms comprising apixaban particles having a D90 less than 100 μm. See, Examples 1 to 5 of Meergans. Meergans does not give single example of any dosage form containing apixaban particles having a D90 particle size of more than 100 μm. The examples

of Meergans followed the established trend of the prior art that for the achievement of consistent human in-vivo dissolution it was essential to use smaller particles of apixaban. In fact, paragraph [0024] of Meergans teaches that it is preferred to use apixaban particles having a D90 in the range from 55 to 100 μm. Based on the disclosure in the examples of Meergans, applicants respectfully submit that it would have been believed that apixaban would have to be provided in particles wherein the D90 value is less than 100 μm.

In contrast, the presently claimed subject matter is based on the finding that apixaban particles having a D90 greater than 100 μm are surprisingly just as bioavailable as the smaller particles and that a dosage form comprising apixaban particles having a D90 more than 100 μm is bioequivalent to the reference listed drug 'ELIQUIS®' of Bristol-Myers Squibb. See Instant Specification, paragraph [0089], and Example 7.

Applicants respectfully submit that the mere reference to D90 value of 90 μm or greater in Meergans would not motivate one of ordinary skill in the art to provide the apixaban particles as described in instant claim 1, particularly in view of the teachings in the art, such as in US9326945, described above, which suggest that apixaban would require use of particles with a D90 of equal to or less than 89 μm for suitable bioavailability. Meergans does not particularly teach apixaban particles with a D90 of more than 100 μm or the bioavailability thereof.

Accordingly, applicants respectfully submit that claim 1 and its dependent claims, claims 2-4, 6-13, 21 and 22 are believed to be distinguishable over Meergans. Given that claim 1 is made clear, and inventively distinguished over the cited reference Meergans, it is asserted that it is also inventively distinguished over Stanic. Applicants respectfully believe that Stanic is being cited with regard to its teachings related to incorporation of a surfactant. Stanic does not cure the deficiencies of Meergans with respect to claim 1. Applicants respectfully request that the rejection of claims 1-4, 6-13, 21 and 22 under 35 U.S.C. § 103 over Meergans in view of Stanic be withdrawn and further requests that claims 1-4, 6-13, 21 and 22 be allowed at this time.

Respectfully submitted,

Date: XXXXXX _____

Attorney for Applicant