Claim No HP-2021-000014

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND & WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT

ASTELLAS PHARMA INC. **Claimant**
(a company incorporated under the laws of Japan)

and

(1) TEVA PHARMACEUTICAL INDUSTRIES LIMITED
(a company incorporated under the laws of Israel)

(2) TEVA UK LIMITED

(3) SANDOZ AG
(a company incorporated under the laws of Switzerland)

(4) SANDOZ LIMITED

Defendants

ANNEX 2 TO THE STATEMENT OF GROUNDS OF AMENDMENT OF EP 2 345 410 B1

CONDITIONAL AMENDMENT 1

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1. A pharmaceutical composition for modified release, comprising: (1) 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-y1)-4'42-[(2-hydroxy-2 phenylethypamino]ethyllacetic acid anilide, or a pharmaceutically acceptable salt thereof, (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and (3) a hydrogel-forming polymer having an average molecular weight of 100,000 to 5,000,000 or a viscosity of ~~12 mPa·s or more in a 5% aqueous solution at 25°C~~, 400 mPa·s or more in a 2% aqueous solution at 25°C and 7,500 mPa·s or less in a 1% aqueous solution at 25°C,

wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol;

wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose; and

wherein the drug dissolution rate from the pharmaceutical composition is 75% or less after 1.5 hours and at least 75% after 7 hours from the beginning of the dissolution test and wherein the dissolution test is carried out in accordance with the paddle method described in the United States

Pharmacopoeia under the conditions that 900 mL of USP buffer, pH 6.8, is used and the paddle rotation speed is 50 to 200 rpm.

2. The pharmaceutical composition for modified release according to claim 1, wherein the paddle rotation speed is 200 rpm.

3. The pharmaceutical composition for modified release according to claim 1, wherein the hydrogel-forming polymer is polyethylene oxide.

4. The pharmaceutical composition for modified release according to any one of claims 1 to 3, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition.

5. The pharmaceutical composition for modified release according to claim 4, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.

6. The pharmaceutical composition for modified release according to any one of claims 1 to 5, wherein an amount of the hydrogel-forming polymer is 1% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.

7. The pharmaceutical composition for modified release according to any one of claims 1 to 6, further comprising an antioxidant.

8. The pharmaceutical composition for modified release according to claim 7, wherein the antioxidant is one compound, or two or more compounds selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate.

9. The pharmaceutical composition for modified release according to claim 8, wherein the antioxidant is butyl hydroxytoluene.

10. The pharmaceutical composition for modified release according to any one of claims 7 to 9, wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight.

11. The pharmaceutical composition for modified release according to any one of claims 1 to 10, further comprising a stabilizer.

12. The pharmaceutical composition for modified release according to claim 11, wherein the stabilizer is one compound, or two or more compounds selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide.

13. The pharmaceutical composition for modified release according to claim 12, wherein the stabilizer is yellow ferric oxide and/or red ferric oxide.

14. The pharmaceutical composition for modified release according to any one of claims 11 to 14, wherein an amount of the stabilizer is 0.05% by weight to 1% by weight.

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ANNEX 3 TO THE STATEMENT OF GROUNDS OF AMENDMENT OF EP 2 345 410 B1

CONDITIONAL AMENDMENT 2

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1. A pharmaceutical composition for modified release, comprising: (1) 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-y1)-4'42-[(2-hydroxy-2 phenylethypamino]ethyllacetic acid anilide, or a pharmaceutically acceptable salt thereof, (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and (3) a hydrogel-forming polymer having an average molecular weight of 100,000 to 5,000,000 or a viscosity of 12 mPa-s or more in a 5% aqueous solution at 25°C, and 7,500 mPa·s or less in a 1% aqueous solution at 25°C,

wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol and wherein the amount of the additive which ensures penetration of water into the pharmaceutical composition is 20% by weight to 60% by weight to the total weight of the pharmaceutical composition;

wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose and wherein the amount of the hydrogel-forming polymer is 10% by weight to 40% by weight with respect to the total weight of the pharmaceutical composition; and

wherein the drug dissolution rate from the pharmaceutical composition is 75% or less after 1.5 hours and at least 75% after 7 hours from the beginning of the dissolution test and wherein the dissolution test is carried out in accordance with the paddle method described in the United States

Pharmacopoeia under the conditions that 900 mL of USP buffer, pH 6.8, is used and the paddle rotation speed is 50 to 200 rpm.

2. The pharmaceutical composition for modified release according to claim 1, wherein the paddle rotation speed is 200 rpm.

3. The pharmaceutical composition for modified release according to claim 1, wherein the hydrogel-forming polymer is polyethylene oxide.

~~4. The pharmaceutical composition for modified release according to any one of claims 1 to 3, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition.~~

~~5. The pharmaceutical composition for modified release according to claim 4, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.~~

~~6. The pharmaceutical composition for modified release according to any one of claims 1 to 5, wherein an amount of the hydrogel-forming polymer is 1% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.~~

~~7~~4**.** The pharmaceutical composition for modified release according to any one of claims 1 to ~~6~~3, further comprising an antioxidant.

~~8~~5**.** The pharmaceutical composition for modified release according to claim ~~7~~4, wherein the antioxidant is one compound, or two or more compounds selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate.

~~9~~6**.** The pharmaceutical composition for modified release according to claim ~~8~~5, wherein the antioxidant is butyl hydroxytoluene.

~~10~~7. The pharmaceutical composition for modified release according to any one of claims ~~7~~4 to ~~9~~6, wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight.

~~11~~8**.** The pharmaceutical composition for modified release according to any one of claims 1 to ~~10~~7, further comprising a stabilizer.

~~12~~9**.** The pharmaceutical composition for modified release according to claim ~~11~~8, wherein the stabilizer is one compound, or two or more compounds selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide.

~~13~~10**.** The pharmaceutical composition for modified release according to claim ~~12~~9, wherein the stabilizer is yellow ferric oxide and/or red ferric oxide.

~~14~~11**.** The pharmaceutical composition for modified release according to any one of claims ~~11~~8 to ~~14~~10, wherein an amount of the stabilizer is 0.05% by weight to 1% by weight.

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ANNEX 4 TO THE STATEMENT OF GROUNDS OF AMENDMENT OF EP 2 345 410 B1

CONDITIONAL AMENDMENT 3

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1. A pharmaceutical composition for modified release, comprising: (1) 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-y1)-4'42-[(2-hydroxy-2 phenylethypamino]ethyllacetic acid anilide, or a pharmaceutically acceptable salt thereof, (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and (3) a hydrogel-forming polymer having an average molecular weight of 100,000 to 5,000,000 or a viscosity of ~~12 mPa·s or more in a 5% aqueous solution at 25°C~~, 400 mPa·s or more in a 2% aqueous solution at 25°C and 7,500 mPa·s or less in a 1% aqueous solution at 25°C,

wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol and wherein the amount of the additive which ensures penetration of water into the pharmaceutical composition is 20% by weight to 60% by weight to the total weight of the pharmaceutical composition;

wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose and wherein the amount of the hydrogel-forming polymer is 10% by weight to 40% by weight with respect to the total weight of the pharmaceutical composition; and

wherein the drug dissolution rate from the pharmaceutical composition is 75% or less after 1.5 hours and at least 75% after 7 hours from the beginning of the dissolution test and wherein the dissolution test is carried out in accordance with the paddle method described in the United States Pharmacopoeia under the conditions that 900 mL of USP buffer, pH 6.8, is used and the paddle rotation speed is 50 to 200 rpm.

2. The pharmaceutical composition for modified release according to claim 1, wherein the paddle rotation speed is 200 rpm.

3. The pharmaceutical composition for modified release according to claim 1, wherein the hydrogel-forming polymer is polyethylene oxide.

~~4. The pharmaceutical composition for modified release according to any one of claims 1 to 3, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition.~~

~~5. The pharmaceutical composition for modified release according to claim 4, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.~~

~~6. The pharmaceutical composition for modified release according to any one of claims 1 to 5, wherein an amount of the hydrogel-forming polymer is 1% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.~~

~~7~~**4.** The pharmaceutical composition for modified release according to any one of claims 1 to ~~6~~3, further comprising an antioxidant.

~~8~~**5.** The pharmaceutical composition for modified release according to claim ~~7~~4, wherein the antioxidant is one compound, or two or more compounds selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate.

~~9~~**6.** The pharmaceutical composition for modified release according to claim ~~8~~5, wherein the antioxidant is butyl hydroxytoluene.

~~10~~7. The pharmaceutical composition for modified release according to any one of claims ~~7~~4 to ~~9~~6, wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight.

~~11~~**8.** The pharmaceutical composition for modified release according to any one of claims 1 to ~~10~~7, further comprising a stabilizer.

~~12~~**9.** The pharmaceutical composition for modified release according to claim ~~11~~8, wherein the stabilizer is one compound, or two or more compounds selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide.

~~13~~**10.** The pharmaceutical composition for modified release according to claim ~~12~~9, wherein the stabilizer is yellow ferric oxide and/or red ferric oxide.

~~14~~**11.** The pharmaceutical composition for modified release according to any one of claims ~~11~~8 to ~~14~~10, wherein an amount of the stabilizer is 0.05% by weight to 1% by weight.

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ANNEX 1 TO THE STATEMENT OF GROUNDS OF AMENDMENT OF EP 2 345 410 B1

UNCONDITIONAL AMENDMENT

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1. A pharmaceutical composition for modified release, comprising: (1) 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-y1)-4'42-[(2-hydroxy-2 phenylethypamino]ethyllacetic acid anilide, or a pharmaceutically acceptable salt thereof, (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and (3) a hydrogel-forming polymer having an average molecular weight of 100,000 to 5,000,000 or a viscosity of 12 mPa-s or more in a 5% aqueous solution at 25°C, and 7,500 mPa-s or less in a 1% aqueous solution at 25°C,

wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol;

wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose; and

wherein the drug dissolution rate from the pharmaceutical composition is 75% or less after 1.5 hours and at least 75% after 7 hours from the beginning of the dissolution test and wherein the dissolution test is carried out in accordance with the paddle method described in the United States Pharmacopoeia under the conditions that 900 mL of USP buffer, pH 6.8, is used and the paddle rotation speed is 50 to 200 rpm.

2. The pharmaceutical composition for modified release according to claim 1, wherein the paddle rotation speed is 200 rpm.

3. The pharmaceutical composition for modified release according to claim 1, wherein the hydrogel-forming polymer is polyethylene oxide.

4. The pharmaceutical composition for modified release according to any one of claims 1 to 3, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition.

5. The pharmaceutical composition for modified release according to claim 4, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.

6. The pharmaceutical composition for modified release according to any one of claims 1 to 5, wherein an amount of the hydrogel-forming polymer is 1% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.

7. The pharmaceutical composition for modified release according to any one of claims 1 to 6, further comprising an antioxidant.

8. The pharmaceutical composition for modified release according to claim 7, wherein the antioxidant is one compound, or two or more compounds selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate.

9. The pharmaceutical composition for modified release according to claim 8, wherein the antioxidant is butyl hydroxytoluene.

10. The pharmaceutical composition for modified release according to any one of claims 7 to 9, wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight.

11. The pharmaceutical composition for modified release according to any one of claims 1 to 10, further comprising a stabilizer.

12. The pharmaceutical composition for modified release according to claim 11, wherein the stabilizer is one compound, or two or more compounds selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide.

13. The pharmaceutical composition for modified release according to claim 12, wherein the stabilizer is yellow ferric oxide and/or red ferric oxide.

14. The pharmaceutical composition for modified release according to any one of claims 11 to 14, wherein an amount of the stabilizer is 0.05% by weight to 1% by weight.