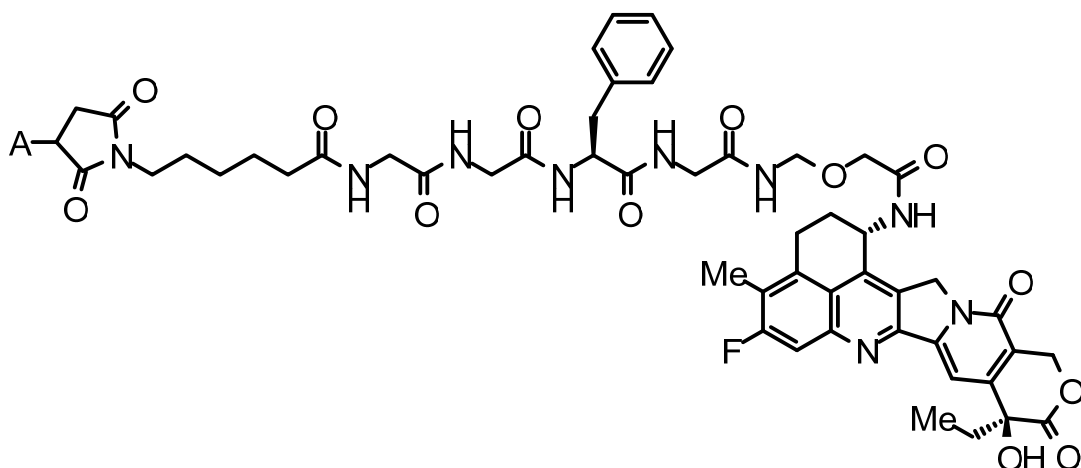


Claims

1. A pharmaceutical composition comprising

- (i) an antibody-drug conjugate,
- (ii) a histidine buffer,
- (iii) sucrose, and
- (iv) polysorbate 80 or polysorbate 20,

wherein the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:



wherein A represents a connecting position to an antibody,

is conjugated to the antibody via a thioether bond, and
wherein the amount of polysorbate 80 or polysorbate 20
is, per 20mg of the antibody-drug conjugate, 0.2 to 0.4
mg, __

wherein the histidine buffer is, per the concentration of
20mg/ml of the antibody-drug conjugate, 3 to 80 mM,

wherein the amount of sucrose is 24 to 320 mg per 20mg of the antibody-drug conjugate,
wherein the pH of the pharmaceutical composition when the antibody-drug conjugate is dissolved in water at a concentration of 20 mg/mL is 4.0 to 7.0.

2. The pharmaceutical composition according to claim 1, wherein the amount of polysorbate 80 or polysorbate 20 is, per 20 mg of the antibody-drug conjugate, 0.2 to 0.3 mg.

3. The pharmaceutical composition according to claim 2, wherein the amount of polysorbate 80 or polysorbate 20 is, per 20 mg of the antibody-drug conjugate, 0.2 or 0.3 mg.

~~4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the amount of sucrose is 24 to 320 mg per 20 mg of the antibody-drug conjugate.~~

54. The pharmaceutical composition according to any one of claims 41 to 3, wherein the amount of sucrose is 90 mg per 20 mg of the antibody-drug conjugate.

65. The pharmaceutical composition according to any one of claims 1 to 54, wherein the histidine buffer is a mixture of L-histidine and L-histidine hydrochloride.

~~76.~~ The pharmaceutical composition according to claim ~~65~~, wherein the histidine buffer is a mixture of L-histidine and L-histidine hydrochloride hydrate.

~~8.~~ ~~The pharmaceutical composition according to any one of claims 1 to 7, wherein the pH of the composition when the antibody-drug conjugate is dissolved in water at a concentration of 20 mg/mL is 4.0 to 7.0.~~

~~97.~~ The pharmaceutical composition according to any one of claims 1 to ~~86~~, wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, or an anti-GPR20 antibody.

~~108.~~ The pharmaceutical composition according to claim ~~97~~, wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

~~119.~~ The pharmaceutical composition according to claim ~~108~~, wherein the anti-HER2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 1 to 449 of SEQ ID NO: 1 and a light chain consisting of an amino acid sequence consisting of amino acid residues 1 to 214 of SEQ ID NO: 2, or an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ

ID NO: 1 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 2.

120. The pharmaceutical composition according to claim 108 or 119, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

131. The pharmaceutical composition according to any one of claims 108 to 120 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.89 mg of L-histidine and 4.04 mg of L-histidine hydrochloride hydrate,
- (iii) 90 mg of sucrose, and
- (iv) 0.3 mg of polysorbate 80.

142. The pharmaceutical composition according to any one of claims 108 to 120 comprising

- (i) 100 mg of the antibody-drug conjugate,
- (ii) 4.45 mg of L-histidine and 20.2 mg of L-histidine hydrochloride hydrate,
- (iii) 450 mg of sucrose, and
- (iv) 1.5 mg of polysorbate 80.

153. The pharmaceutical composition according to claim 97, wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

~~164~~4. The pharmaceutical composition according to claim ~~153~~3, wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

~~175~~5. The pharmaceutical composition according to claim ~~153~~3 or ~~164~~4, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

~~186~~6. The pharmaceutical composition according to any one of claims ~~153~~3 to ~~175~~5 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.81 mg of L-histidine and 4.14 mg of L-histidine hydrochloride hydrate,
- (iii) 90 mg of sucrose, and
- (iv) 0.3 mg of polysorbate 20.

~~197~~7. The pharmaceutical composition according to any one of claims ~~153~~3 to ~~175~~5 comprising

- (i) 100 mg of the antibody-drug conjugate,
- (ii) 4.06 mg of L-histidine and 20.7 mg of L-histidine hydrochloride hydrate,

- (iii) 450 mg of sucrose, and
- (iv) 1.5 mg of polysorbate 20.

~~20~~18. The pharmaceutical composition according to claim ~~97~~, wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

~~21~~9. The pharmaceutical composition according to claim ~~20~~18, wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

~~22~~0. The pharmaceutical composition according to claim ~~20~~18 or ~~21~~9, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3 to 5.

~~23~~1. The pharmaceutical composition according to any one of claims ~~20~~18 to ~~22~~0 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.78 mg of L-histidine and 1.05 mg of L-histidine hydrochloride hydrate,

- (iii) 90 mg of sucrose, and
- (iv) 0.2 or 0.3 mg of polysorbate 80.

242. The pharmaceutical composition according to any one of claims ~~20~~18 to 220 comprising

- (i) 100 mg of the antibody-drug conjugate,
- (ii) 3.88 mg of L-histidine and 5.26 mg of L-histidine hydrochloride hydrate,
- (iii) 450 mg of sucrose, and
- (iv) 1.0 or 1.5 mg of polysorbate 80.

253. The pharmaceutical composition according to claim ~~9~~7, wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

264. The pharmaceutical composition according to claim ~~25~~3, wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 8, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

275. The pharmaceutical composition according to claim ~~25~~3 or 264, wherein the average number of units of the

drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3 to 5.

~~28~~6. The pharmaceutical composition according to any one of claims ~~25~~3 to ~~27~~5 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.65 mg of L-histidine and 1.22 mg of L-histidine hydrochloride hydrate,
- (iii) 90 mg of sucrose, and
- (iv) 0.2 or 0.3 mg of polysorbate 20.

~~29~~7. The pharmaceutical composition according to any one of claims ~~25~~3 to ~~27~~5 comprising

- (i) 100 mg of the antibody-drug conjugate,
- (ii) 3.23 mg of L-histidine and 6.12 mg of L-histidine hydrochloride hydrate,
- (iii) 450 mg of sucrose, and
- (iv) 1.0 or 1.5 mg of polysorbate 20.

~~30~~28. The pharmaceutical composition according to claim ~~9~~7, wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

~~31~~29. The pharmaceutical composition according to claim ~~30~~28, wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of

SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

320. The pharmaceutical composition according to claim ~~3028~~ or ~~3129~~, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

331. The pharmaceutical composition according to any one of claims ~~3028~~ to 320 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.32 mg of L-histidine and 1.66 mg of L-histidine hydrochloride hydrate,
- (iii) 90 mg of sucrose, and
- (iv) 0.3 mg of polysorbate 80.

342. The pharmaceutical composition according to any one of claims ~~3028~~ to 320 comprising

- (i) 100 mg of the antibody-drug conjugate,
- (ii) 1.62 mg of L-histidine and 8.29 mg of L-histidine hydrochloride hydrate,
- (iii) 450 mg of sucrose, and
- (iv) 1.5 mg of polysorbate 80.

~~35~~3. The pharmaceutical composition according to any one of claims 1 to ~~34~~2, wherein the composition is in the form of an injection.

~~36~~4. The pharmaceutical composition according to claim ~~35~~3, wherein the composition is in the form of an aqueous injection.

~~37~~5. The pharmaceutical composition according to claim ~~36~~4, wherein the concentration of the antibody-drug conjugate is 20 mg/mL.

~~38~~6. The pharmaceutical composition according to claim ~~36~~4 or ~~37~~5, wherein the composition is frozen.

~~39~~7. The pharmaceutical composition according to claim ~~35~~3, wherein the composition is in the form of a lyophilized injection.

~~40~~38. The pharmaceutical composition according to claim ~~39~~7, wherein the composition is stored in a brown vial.

~~41~~39. The pharmaceutical composition according to any one of claims 1 to ~~40~~38, for use in therapy.

420 Use of the pharmaceutical composition according to any one of claims 1 to 4038, for the preparation of a medicament for treating cancer.

431. A method for producing a pharmaceutical composition according to claim 397, comprising the steps of:

(1) preparing an aqueous solution comprising predetermined amounts of

(i) an antibody-drug conjugate,

(ii) a histidine buffer,

(iii) sucrose, and

(iv) polysorbate 80 or polysorbate 20,

(2) if necessary, adjusting the pH of the aqueous solution to a predetermined value, and then

(3) lyophilizing the aqueous solution.

442. The production method according to claim 431, wherein the step of lyophilizing the aqueous solution comprises a process of annealing at a shelf temperature which is near the eutectic point of the aqueous solution, wherein near the eutectic point indicates the range of from a temperature which is 1.5°C lower than the eutectic point to a temperature which is 1.5°C higher than the eutectic point.

453. The production method according to claim 442, characterized in that the time for a process of primary

drying is shortened compared with that when annealing at a shelf temperature which is 5°C lower than the eutectic point is performed.

464. The production method according to claim 442 or 453, characterized in that a lyophilized cake having less shrinkage is obtained compared with that when annealing at a shelf temperature which is 5°C lower than the eutectic point is performed.

475. The production method according to claim 431, wherein the step of lyophilizing the aqueous solution comprises a process of performing annealing at a shelf temperature of -4 to -1°C.

486. The production method according to claim 475, wherein the step of lyophilizing the aqueous solution further comprises a process of primary drying at a shelf temperature of -5 to 5°C under a vacuum of 5 to 15 Pa.

497. The production method according to claim 486, wherein the step of lyophilizing the aqueous solution further comprises a process of secondary drying at a shelf temperature of 40 to 50°C under a vacuum of 5 to 15 Pa.