

Claims:

[Claim 1]. A stable liquid pharmaceutical formulation, the formulation comprising a glucagon-like peptide 2 (GLP-2) analogue, wherein the GLP-2 analogue is represented by the formula:

5 R^1 -Z¹-His-Gly-Glu-Gly-X⁵-Phe-Ser-Ser-Glu-Leu-X¹¹-Thr-Ile-Leu-Asp-Ala-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Ala-Trp-Leu-Ile-Ala-Thr-Lys-Ile-Thr-Asp-Z²-R²

wherein:

R¹ is hydrogen, C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl;

X⁵ is Ser or Thr;

10 X¹¹ is Ala or Ser;

R² is NH₂ or OH; and

Z¹ and Z² are independently absent or a peptide sequence of 1-6 amino acid units of Lys;

or a pharmaceutically acceptable salt or derivative thereof;

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wherein the formulation comprises the GLP-2 analogue at a concentration of about 20 mg/mL, histidine buffer at a concentration of about 15 mM, mannitol as a non-ionic tonicity modifier at a concentration of about 230 mM, and arginine q.s. to provide a pH of about 7.0;

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~~(a) the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL;~~

~~(b) a buffer selected from the group consisting of a histidine buffer, mesylate buffer, acetate buffer, glycine buffer, lysine buffer, TRIS buffer, Bis-Tris buffer and MOPS buffer, the buffer being present at a concentration of about 5 mM to about 50 mM;~~

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~~(c) a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol, sorbitol and trehalose at a concentration of about 90 mM to about 360 mM; and~~

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~~(d) arginine q.s. to provide a formulation having a pH of about 6.6 to about 7.4 preferably, wherein the arginine acid is L-arginine/acetic acid;~~

wherein the formulation contains 5% or less of the GLP-2 analogue in the form of covalently bonded oligomeric products.

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[Claim 2]. The formulation according to claim 1, wherein the total acetate concentration arising from the GLP2 analogue in the formulation is less than or equal to 11% acetate per mg GLP-2 analogue, and/or wherein formation of covalently linked oligomers of the GLP-2 analogue is inversely dependent on the concentration of the GLP-2 analogue in the formulation.

[Claim 3]. The formulation according to any one of claim 1 or 2, wherein the formulation

a) is an aqueous formulation;

b) is stable for at least 18 months when stored at 2-8°C;

c) has a viscosity between 0.8 and 2.0 mPa/sec measured at 25°C;

5 d) is a ready-to-use formulation;

~~e) has a pH of about 6.8 to about 7.2 preferably has a pH of about 7.0;~~

~~ef) is free of reducing agent;~~

~~fg) is stable at 2-8°C for at least 6 months, at least 12 months, at least 18 months or at least 24 months; and/or~~

10 ~~gh) is sterile.~~

[Claim 4]. The formulation according to any one of the preceding claims, ~~wherein the GLP-2 analogue is present in the formulation at a concentration of about 15 mg/mL to about 25 mg/ml, preferably wherein the GLP-2 analogue is present in the formulation at a concentration of about 20 mg/mL; and/or~~ wherein the GLP-2 analogue in the formulation retains at least about 90% of its biological activity after 18 months of storage 2-8°C.

[Claim 5]. The formulation according to any one of the preceding claims, ~~wherein the buffer is~~

20 ~~a) present in the formulation at a concentration of about 5 mM to about 25 mM; and/or~~

~~b) a histidine buffer, preferably wherein the histidine buffer is present in the formulation at a concentration of about 15 mM and/or preferably wherein the histidine buffer is L-histidine.~~

[Claim 6]. The formulation according to any one of the preceding claims, ~~wherein the non-ionic tonicity modifier is~~

25 ~~a) present in the formulation at a concentration of about 150 mM to about 250 mM; and/or~~

~~b) is mannitol, preferably wherein the mannitol is present in the formulation at a concentration of about 230 mM and/or preferably wherein the mannitol is D-mannitol.~~

30 ~~7. The formulation according to any one of the preceding claims, wherein the formulation comprises the GLP-2 analogue at a concentration of about 20 mg/mL, histidine buffer at a concentration of about 15 mM, mannitol at a concentration of about 230 mM, and arginine q.s. to provide a pH of about 7.0, preferably wherein the histidine buffer is L-histidine and/or preferably wherein the mannitol is D-mannitol or optionally consists of the GLP-2~~
35 ~~analogue at a concentration of about 2 mg/mL to about 30 mg/ml, a buffer selected from the group consisting of a histidine buffer, mesylate buffer and~~

5 ~~acetate buffer, the buffer being present at a concentration of about 5 mM to about 50 mM, a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol and sorbitol at a concentration of about 90 mM to about 360 mM, arginine q.s. to provide a pH of about 6.6 to about 7.4, preferably wherein the histidine buffer is L-histidine and/or preferably wherein the mannitol is D-mannitol.~~

[Claim 78]. The formulation according to any one of the preceding claims, wherein the formulation is to be administered by injection, preferably subcutaneous injection.

10 [Claim 89]. The formulation according to any one of the preceding claims, wherein the GLP-2 analogue is provided as an acetate salt, preferably wherein the GLP-2 analogue is ZP1848 or ZP1848-acetate, and/or preferably wherein the formulation consist of ZP1848-acetate at a concentration of about 20 mg/mL, histidine buffer at a concentration of about 15 mM, mannitol at a concentration of about 230 mM, and arginine q.s. to provide a pH of about 7.0.

15 [Claim 94]. An article of manufacture or a kit comprising a container holding the stable pharmaceutical formulation of any one of claims 1 to 98.

20 [Claim 104]. A delivery device containing a liquid formulation comprising a GLP-2 analogue of any one of claims 1 to 89, optionally wherein the delivery device is pre-filled syringe, an injector device, an injector pen, an adjustable dose auto-injector, a disposable auto-injector, a wearable injector, an infusion pump.

25 [Claim 114]. A formulation of the glucagon-like peptide 2 (GLP-2) analogue of any one of claims 1 to 89 for use in therapy, preferably wherein the GLP-2 analogue is to be administered once weekly or twice weekly.

30 [Claim 124]. A formulation of the glucagon-like peptide 2 (GLP-2) analogue of any one of claims 1 to 89 for use in treatment and/or prevention of a stomach and bowel-related disorder in a human patient, preferably wherein the GLP-2 analogue is to be administered once weekly or twice weekly.

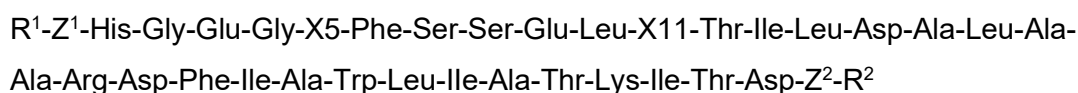
35 [Claim 134]. The formulation of the glucagon-like peptide 2 (GLP-2) analogue for use according to claim 124, wherein the stomach and bowel-related disorder is ulcers, digestion disorders, malabsorption syndromes, short-gut syndrome, cul-de-sac syndrome, inflammatory bowel disease, celiac sprue (for example arising from gluten induced enteropathy or celiac

disease), tropical sprue, hypogammaglobulinemic sprue, enteritis, regional enteritis (Crohn's disease), ulcerative colitis, small intestine damage or short bowel syndrome (SBS), SBS-intestinal failure, being on the border between being a patient having SBS-intestinal insufficiency and SBS-intestinal failure, radiation enteritis, infectious or post-infectious enteritis, or small intestinal damage due to toxic or other chemotherapeutic agents.

[Claim 1445]. The formulation of the glucagon-like peptide 2 (GLP-2) analogue for use according to claim 1314, wherein the GLP-2 analogue is combined with one or more anti-cancer therapies, preferably wherein the one or more anti-cancer therapy comprises one or more chemotherapeutic agent(s) or radiation therapy.

[Claim 1546]. The formulation of the glucagon-like peptide 2 (GLP-2) analogue for use according to claim 1445, wherein the formulation is used in the treatment and/or prevention of a side effect of chemotherapy or radiation treatment, preferably wherein the side effect of chemotherapy is diarrhoea, abdominal cramping, vomiting or structural and functional damage of the intestinal epithelium resulting from chemotherapy treatment.

[Claim 1647]. A process for producing a stable liquid pharmaceutical formulation comprising a glucagon-like peptide 2 (GLP-2) analogue, wherein the GLP-2 analogue is represented by the formula:



wherein:

R¹ is hydrogen, C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl

X5 is Ser or Thr

X11 is Ala or Ser

R² is NH₂ or OH;

Z¹ and Z² are independently absent or a peptide sequence of 1-6 amino acid units of Lys; or a pharmaceutically acceptable salt or derivative thereof, preferably wherein the total

acetate concentration arising from the GLP2 analogue in the formulation is less than or equal to 11% acetate per mg GLP-2 analogue;

wherein the process comprising formulating (a) the GLP-2 analogue at a concentration of about 20 mg/mL ~~the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL~~, (b) histidine buffer at a concentration of about 15 mM ~~with a buffer selected from the group consisting of a histidine buffer, mesylate buffer, acetate buffer, glycine buffer, lysine buffer, TRIS buffer, Bis-Tris buffer and MOPS buffer, the buffer being present at a concentration of about 5 mM to~~

about 50 mM; (c) mannitol as a non-ionic tonicity modifier at a concentration of about 230 mM with ~~a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol, sorbitol and trehalose, the non-ionic tonicity modifier being present at a concentration of about 90 mM to about 360 mM~~; and (d) with arginine q.s. to provide a pH of about 7.0 ~~arginine q.s. to provide a formulation having a pH of about 6.6 to about 7.4~~;

wherein the formulation contains 5% or less of the GLP-2 analogue in the form of covalently bonded oligomeric products, preferably wherein formation of covalently linked oligomers of the GLP-2 analogue is inversely dependent on the concentration of the GLP-2 analogue in the formulation.

[Claim 1748]. The process according to claim 1647, wherein the formulation is stable for at least 18 months when stored at 2-8°C, and/or wherein the formulation has a viscosity greater than 0.8 and lower than or equal to 2.0 mPa/sec measured at 25°C.

[Claim 1849]. Use of a formulation comprising a glucagon-like peptide 2 (GLP-2) analogue, wherein the GLP-2 analogue is represented by the formula:

R¹-Z¹-His-Gly-Glu-Gly-X5-Phe-Ser-Ser-Glu-Leu-X11-Thr-Ile-Leu-Asp-Ala-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Ala-Trp-Leu-Ile-Ala-Thr-Lys-Ile-Thr-Asp-Z²-R²

wherein:

R¹ is hydrogen, C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl

X5 is Ser or Thr

X11 is Ala or Ser

R² is NH₂ or OH;

Z¹ and Z² are independently absent or a peptide sequence of 1-6 amino acid units of Lys; or a pharmaceutically acceptable salt or derivative thereof, preferably wherein the total acetate concentration arising from the GLP2 analogue in the formulation is less than or equal to 11% acetate per mg GLP-2 analogue;

for providing an liquid pharmaceutical formulation which is stable for 24 months when stored at 2-8°C, wherein the formulation comprises the GLP-2 analogue at a concentration of about 20 mg/mL, histidine buffer at a concentration of about 15 mM, mannitol as a non-ionic tonicity modifier at a concentration of about 230 mM, and arginine q.s. to provide a pH of about 7.0;

~~(a) the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL;~~

~~(b) a buffer selected from the group consisting of a histidine buffer, mesylate buffer, acetate buffer, glycine buffer, lysine buffer, TRIS buffer, Bis-Tris buffer and MOPS buffer, the buffer being present at a concentration of about 5 mM to about 50 mM;~~

~~(c) a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol, sorbitol and trehalose at a concentration of about 90 mM to about 360 mM; and~~

~~(d) arginine q.s. to provide a formulation having a pH of about 6.6 to about 7.4;~~

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wherein the formulation contains 5% or less of the GLP-2 analogue in the form of covalently bonded oligomeric products, preferably wherein formation of covalently linked oligomers of the GLP-2 analogue is inversely dependent on the concentration of the GLP-2 analogue in the formulation; and/or

10 wherein the formulation has a viscosity between 0.8 and 2.0 mPa/sec measured at 25°C.

[Claim 1920]. An *in vitro* method for modulating the viscosity of a stable liquid pharmaceutical formulation comprising a glucagon-like peptide 2 (GLP-2) analogue, wherein the GLP-2 analogue is represented by the formula:

15 $R^1-Z^1\text{-His-Gly-Glu-Gly-X5-Phe-Ser-Ser-Glu-Leu-X11-Thr-Ile-Leu-Asp-Ala-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Ala-Trp-Leu-Ile-Ala-Thr-Lys-Ile-Thr-Asp-Z}^2\text{-R}^2$

wherein:

R¹ is hydrogen, C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl

20 X5 is Ser or Thr

X11 is Ala or Ser

R² is NH₂ or OH;

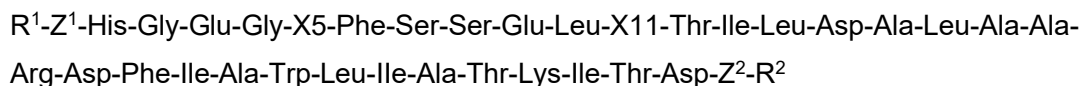
Z¹ and Z² are independently absent or a peptide sequence of 1-6 amino acid units of Lys; or a pharmaceutically acceptable salt or derivative thereof;

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wherein the method comprises formulating (a) the GLP-2 analogue at a concentration of about 20 mg/mL, (b) histidine buffer at a concentration of about 15 mM; (c) mannitol as a non-ionic tonicity modifier at a concentration of about 230 mM; and (d) with arginine q.s. to provide a pH of about 7.0;~~(a) the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL, (b) with a buffer selected from the group consisting of a histidine buffer, mesylate buffer, acetate buffer, glycine buffer, lysine buffer, TRIS buffer, Bis-Tris buffer or MOPS buffer, the buffer being present at a concentration of about 5 mM to about 50 mM; (c) with a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol, sorbitol and trehalose, the non-ionic tonicity modifier being present at a concentration of about 90 mM to about 360 mM; and (d) with arginine q.s. to~~
30 ~~provide a formulation having a pH of about 6.6 to about 7.4;~~
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wherein the total acetate concentration arising from the GLP2 analogue in the formulation is less than or equal to 11% acetate per mg GLP-2 analogue and wherein the formulation has a viscosity greater than 0.8 and lower than or equal to 2.0 mPa/sec measured at 25°C.

[Claim 2024]. An *in vitro* method for reducing the formation of covalently bonded oligomeric products of a glucagon-like peptide 2 (GLP-2) analogue in a stable liquid pharmaceutical formulation comprising a GLP-2 analogue represented by the formula:



wherein:

R¹ is hydrogen, C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl

X5 is Ser or Thr

X11 is Ala or Ser

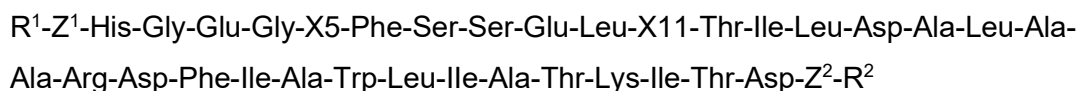
R² is NH₂ or OH;

Z¹ and Z² are independently absent or a peptide sequence of 1-6 amino acid units of Lys; or a pharmaceutically acceptable salt or derivative thereof;

wherein the method comprises formulating (a) the GLP-2 analogue at a concentration of about 20 mg/mL, (b) histidine buffer at a concentration of about 15 mM; (c) mannitol as a non-ionic tonicity modifier at a concentration of about 230 mM; and (d) with arginine q.s. to provide a pH of about 7.0; ~~(a) the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL, (b) with a buffer selected from the group consisting of a histidine buffer, mesylate buffer, acetate buffer, glycine buffer, lysine buffer, TRIS buffer, Bis-Tris buffer or MOPS buffer, the buffer being present at a concentration of about 5 mM to about 50 mM; (c) with a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol, sorbitol and trehalose, the non-ionic tonicity modifier being present at a concentration of about 90 mM to about 360 mM; and (d) with arginine q.s. to provide a formulation having a pH of about 6.6 to about 7.4;~~

wherein the formulation contains 5% or less of the GLP-2 analogue in the form of covalently bonded oligomeric products, preferably wherein formation of covalently linked oligomers of the GLP-2 analogue is inversely dependent on the concentration of the GLP-2 analogue in the formulation.

[Claim 2122]. Use of a formulation for reducing the formation of covalently bonded oligomeric products of a glucagon-like peptide 2 (GLP-2) analogue, wherein the GLP-2 analogue is represented by the formula:



wherein:

R¹ is hydrogen, C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl

X5 is Ser or Thr

X11 is Ala or Ser

R² is NH₂ or OH;

Z¹ and Z² are independently absent or a peptide sequence of 1-6 amino acid units of Lys;
or a pharmaceutically acceptable salt or derivative thereof;

in an liquid pharmaceutical formulation which is stable for 24 months when stored at 2-8°C,
wherein the formulation comprises the GLP-2 analogue at a concentration of about 20
mg/mL, histidine buffer at a concentration of about 15 mM, mannitol as a non-ionic tonicity
modifier at a concentration of about 230 mM, and arginine q.s. to provide a pH of about 7.0;

~~(a) the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL;~~

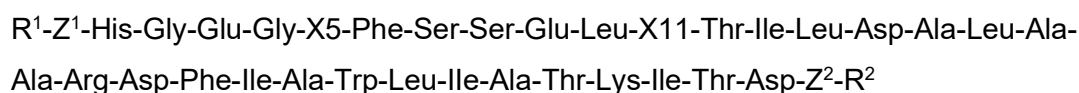
~~(b) a buffer selected from the group consisting of a histidine buffer, mesylate buffer, acetate buffer,
glycine buffer, lysine buffer, TRIS buffer, Bis-Tris buffer and MOPS buffer, the buffer being present at
a concentration of about 5 mM to about 50 mM;~~

~~(c) a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol,
sorbitol and trehalose at a concentration of about 90 mM to about 360 mM; and~~

~~(d) arginine q.s. to provide a formulation having a pH of about 6.6 to about 7.4;~~

wherein the formulation contains 5% or less of the GLP-2 analogue in the form of covalently
bonded oligomeric products, preferably wherein formation of covalently linked oligomers of
the GLP-2 analogue is inversely dependent on the concentration of the GLP-2 analogue in
the formulation.

[Claim 2223]. Use of a formulation for modulating the viscosity of a liquid pharmaceutical
formulation comprising a glucagon-like peptide 2 (GLP-2) analogue, wherein the GLP-2
analogue is represented by the formula:



wherein:

R¹ is hydrogen, C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl

X5 is Ser or Thr

X11 is Ala or Ser

R² is NH₂ or OH;

Z¹ and Z² are independently absent or a peptide sequence of 1-6 amino acid units of Lys;
or a pharmaceutically acceptable salt or derivative thereof;

in an liquid pharmaceutical formulation which is stable for 24 months when stored at 2-8°C, wherein the formulation comprises the GLP-2 analogue at a concentration of about 20 mg/mL, histidine buffer at a concentration of about 15 mM, mannitol as a non-ionic tonicity modifier at a concentration of about 230 mM, and arginine q.s. to provide a pH of about 7.0;

~~(a) the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL;~~

~~(b) a buffer selected from the group consisting of a histidine buffer, mesylate buffer, acetate buffer, glycine buffer, lysine buffer, TRIS buffer, Bis-Tris buffer and MOPS buffer, the buffer being present at a concentration of about 5 mM to about 50 mM;~~

~~(c) a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol, sorbitol and trehalose at a concentration of about 90 mM to about 360 mM; and~~

~~(d) arginine q.s. to provide a formulation having a pH of about 6.6 to about 7.4;~~

wherein the total acetate concentration arising from the GLP2 analogue in the formulation is less than or equal to 11% acetate per mg GLP-2 analogue and the formulation has a viscosity between 0.8 and 2.0 mPa/sec measured at 25°C.

[Claim 2324]. A solid composition comprising an acetate salt of a glucagon-like peptide 2 (GLP-2) analogue having the formula:

(H-HGEGTFSSSELATILDALAARDFIAWLIATKITDKKKKKK-NH₂), x(CH₃COOH) or

(H-HGEGSFSSSELSTILDALAARDFIAWLIATKITDKKKKKK-NH₂), x(CH₃COOH).

where x is selected from any one of from 1.0 to 8.0 from 4.0 to 6.0, from 2.0 to 7.0, from 3.0 to 6.0, from 4.0 to 6.0, and from 4.0 to 8.0.

[Claim 2425]. A stable aqueous pharmaceutical formulation, the formulation comprising (a) the solid composition of claims 24 23 at a concentration of ~~about~~ 2 mg/mL to ~~about~~ 30 mg/mL;

(b) a buffer selected from the group consisting of a histidine buffer, mesylate buffer, acetate buffer, glycine buffer, lysine buffer, TRIS buffer, Bis-Tris buffer and MOPS buffer, the buffer being present at a concentration of ~~about~~ 5 mM to ~~about~~ 50 mM;

(c) a non-ionic tonicity modifier selected from the group consisting of mannitol, sucrose, glycerol, sorbitol and trehalose at a concentration of ~~about~~ 90 mM to ~~about~~ 360 mM; and

(d) arginine q.s. to provide a formulation having a pH of ~~about~~ 6.6 to ~~about~~ 7.4;

wherein the formulation contains 5% or less of the GLP-2 analogue in the form of covalently bonded oligomeric products and wherein the formulation has a viscosity between 0.8 and 2.0 mPa/sec measured at 25°C.

[Claim 25]~~26~~. The formulation of claim 24~~25~~, wherein the formulation is stable for at least 18 months when stored at 2-8°C, and/or wherein the GLP-2 analogue in the formulation retains at least about 90% of its biological activity after 18 months of storage 2-8°C.

[Claim 26]. The formulation of claim 24 or claim 25, wherein the formulation comprises the GLP-2 analogue at a concentration of about 20 mg/mL, histidine buffer at a concentration of about 15 mM, mannitol as a non-ionic tonicity modifier at a concentration of about 230 mM, and arginine q.s. to provide a pH of about 7.0.