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A one dose syringe, comprising a freeze-dried protein composition, for administering of a volume less than 0.5 ml

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<p>(21) International Application Number: PCT/SE98/02096 (22) International Filing Date: 19 November 1998 (19.11.98) (30) Priority Data: 9704405-1 28 November 1997 (28.11.97) SE (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN AB [SE/SE]; S-112 87 Stockholm (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LIMRELL, Karin [SE/SE]; Gransångarevägen 5, S-192 55 Sollentuna (SE). FLORIN-ROBERTSSON, Ebba [SE/SE]; Norrtullsgatan 12 E, S-113 27 Stockholm (SE). HÖKBY, Elvy [SE/SE]; Bergkantsvägen 18, S-122 32 Enskede (SE). NILSSON, Ulf [SE/SE]; Ekuddsvägen 16 B, S-178 34 Ekerö (SE). STRÖM, Anders [SE/SE]; Tätörpsvägen 14 A, S-122 57 Enskede (SE). (74) Agents: TANNERFELDT, Agneta et al.; Pharmacia & Upjohn AB, S-112 87 Stockholm (SE).</p>	<p>(81) Designated States: AU, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU, SK, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.  </p>	
<p>(54) Title: A ONE DOSE SYRINGE, COMPRISING A FREEZE-DRIED PROTEIN COMPOSITION, FOR ADMINISTERING OF A VOLUME LESS THAN 0.5 ml</p>		
<p>(57) Abstract The invention relates to a one-dose syringe comprising a first chamber with a freeze-dried composition comprising a protein in an amount of less than 1.4 mg, amino acid and stabilizer where the weight ratio between protein and amino acid versus stabilizer is less than 1.5 and in which the ratio of the weight of the dry component versus the cake volume in the first chamber is above 12 mg/ml and a second chamber with an aqueous reconstitution solution with an injectable volume of less than 0.5 ml.</p>		

A ONE DOSE SYRINGE, COMPRISING A FREEZE-DRIED PROTEIN COMPOSITION, FOR ADMINISTERING OF A VOLUME LESS THAN 0.5 ml

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Introduction

The present invention relates to a one-dose syringe comprising a first chamber with a freeze-dried composition comprising a protein in an amount of less than 1.4 mg, amino acid and stabilizer where the weight ratio between protein and amino acid versus stabilizer
10 is less than 1.5 and in which the ratio of the weight of the dry component versus the cake volume in the first chamber is above 12 mg/ml and a second chamber with an aqueous reconstitution solution with an injectable volume of less than 0.5 ml.

Prior art

15 Proteins, which often are sensitive to storage in liquids, are normally freeze-dried and reconstituted by the patient shortly before injection.

When preparing such a syringe with a therapeutical amount of a protein for the patient, important criteria are:

- Acceptable stability of the powder before reconstitution. The preparation should have at
20 least as good quality as freeze-dried products on the market. The dried product should be able to be stored in room temperature, at least for a certain time.
- No pain when given to patients, e.g. by using an isotonic solution and a small injection volume.
- Acceptable reconstitution time.

A device for preparation of an injectable solution of substances sensitive to degradation is described in US4968 299, and which is named KabiPen® on the market. With KabiPen® the patient has got a device which is rather simple to handle. The device
5 comprises a two-chamber ampoule Genomix® containing hGH (human Growth Hormone) as a lyophilized powder in one of the compartments and a reconstitution solution in the other. The patient reconstitutes the product before use. The reconstituted product is then stable for 3 weeks when stored at 2-8°C. This device is a multiple-dose syringe.

10 On the market there is also a one dose device for growth hormone, KabiQuick®, which has an injection volume of 0.5 ml or more.

In the patent application WO 89/09614, Genentech, a stabilized formulation of hGH comprising glycine, mannitol and a buffer is disclosed and in a preferred embodiment a non-ionic surfactant such as polysorbate 80 is added. Sodium-phosphate is suggested as
15 buffer substance. The formulation has an increased stability in a lyophilized formulation and upon reconstitution. The final ratio of the ingredients is obtained by buffer exchange on a gel filtration column.

Nothing is mentioned about the volume injected to the patient, nor the amount of the protein.

20 In the patent application WO 91/18621 (GENENTECH) mannitol is generally mentioned as carrier for stability of GH and IGF.

The patent application WO 94/03198 (GENENTECH) discloses an aqueous formulation with GH + buffer + surfactant + mannitol.

There has been a desire to find a one dose syringe, which has an injectable volume of less than 0.5 ml and a low amount of protein per dose and which can be produced by freeze-drying without production problem.

It was noticed that when a one-dose syringe with protein in a low amount in a small
5 injection volume was produced, problems arise when the solution in the first chamber of the syringe is freeze-dried.

The matrix of the freeze-dried cake was non-coherent, and this resulted surprisingly in blow out. The cake bursted in the chamber and the protein was thus lost. This is not acceptable, not only for production reason, but also for economical reasons when a
10 medicament including an expensive protein is produced. A solution to this problem must therefore be found.

This problem does not occur when KabiQuick or other freeze-dried protein products are prepared. It was noticed that these products have a high amount of protein and amino acid. The problem arising for a low amount of protein per dose has now been solved by the
15 present invention.

The invention

We have now found that one possible way to produce the desired one dose syringe with a low amount of protein and a small injectable volume, is to combine the amount of growth
20 hormone, the dry content and ratio of content of the protein and the additional components according to the annexed claims.

The present invention relates thus to a one-dose syringe comprising a first chamber with a freeze-dried composition comprising a protein in an amount of less than 1.4 mg, amino acid and stabilizer where the weight ratio between protein and amino acid versus stabilizer

is less than 1.5 and in which the ratio of the weight of the dry component versus the cake volume in the first chamber is above 12 mg/ml and a second chamber with an aqueous reconstitution solution with an injectable volume of less than 0.5 ml.

This claimed new device with the new composition can be produced without complications
5 and stored with good stability.

The weight ratio between protein and amino acid versus stabilizer is preferably equal to or less than 1.3. The aqueous reconstitution solution has preferably an injectable volume of less than 0.3ml. The solution may contain a preservative and or a buffer.

By stabilizer is meant a bulking agent matrix builder and/or cake former, e.g. mannitol but
10 not an amino acid and by amino acid is preferably glycine used but other amino acids such as alanine can also be used.

By isotonic agent is meant a substance for achieving the right osmolality of the injection solution.

15 The protein is preferably growth hormone, recombinant or nature, which can be both human and animal such as human growth hormone (hGH), bovine growth hormone (bGH) and porcine growth hormone (pGH).

HGH, is a protein consisting of a single chain of 191 amino acids. The molecule is cross-
20 linked by two disulphide bridges and the monomeric form has a molecular weight of 22 kDa.

Two types of therapeutically useful recombinant hGH preparations are present on the market: the authentic one, e.g. Genotropin®, Pharmacia & Upjohn AB, and an analogue with an additional methionine residue at the N-terminal end, e.g. Somatonorm®.

25



hGH is used to stimulate linear growth in patients with hypo pituitary dwarfism or Turner's syndrome but other indications have also been suggested.

5 EXAMPLES

The invention is described in the following example with different formulations A-K in which different compositions and volumes were freeze-dried, see tables below.

In the examples below a recombinant produced hGH has been used (GH).

The solution of hGH for filling is obtained from the final gel filtration step of the bulk
10 solution purification process. Buffer is added for adjustment of the final excipient concentration and thereafter the solution is diluted with buffer to the correct protein concentration.

By cake volume is meant dispensed volume before freeze-drying. The solvent used is water.

15

Examples F, I and K are according to the invention.

Formulation	A	B
<i>First chamber, mg/cylinder</i>		
GH	0,35	0,34
Glycine	0,19	0,23
Mannitol	0,95	1,14
Sodium phosphate	0,02	0,05
Disodium phosphate	0,01	0,03
Cake volume, ml	0,25	0,3
Weight of dry substances, mg	1,5	1,8
Ratio weight/cake volume	6,1	6,0
<i>Weight ratio</i>		
GH+Glycine	0,539	0,570
Mannitol	0,950	1,140
(GH+Glycine):Mannitol	0,567	0,5
<i>Cake observation</i>	Blow out	Blow out

The formulations A and B resulted in blow out.

- 5 In order to avoid the blow out problem the weight/cake volume ratio was raised by addition of mannitol, see table below.

Formulation	C	D	E
<i>First chamber, mg/cylinder</i>			
GH	0,33	0,31	0,33
Glycine	0,23	0,23	0,23
Mannitol	1,37	2,67	1,14
Sodium phosphate	0,05	0,05	0,05
Disodium phosphate	0,03	0,03	0,03
Cake volume, ml	0,3	0,3	0,3
Weight of dry substances, mg	2,0	3,3	1,8
Ratio weight/cake volume	6,7	11,0	5,9
<i>Weight ratio</i>			
GH+Glycine	0,560	0,541	0,560
Mannitol	1,374	2,670	1,140
(GH+Glycine):Mannitol	0,407	0,202	0,491
<i>Cake observation</i>	Blow out	Blow out	Blow out

However, the problem with blow out remained. The formulations C, D and E resulted all in blow out.

5 Instead the cake volume was lowered in order to increase the weight/cake volume ratio.

Formulation	F	G	H
<i>First chamber, mg/cylinder</i>			
GH	0,32	0,33	0,32
Glycine	0,33	0,23	0,23
Mannitol	1,65	1,14	1,14
Sodium phosphate	0,05	0,05	0,05
Disodium phosphate	0,03	0,03	0,03
Cake volume, ml	0,1	0,15	0,2
Weight of dry substances, mg	2,4	1,8	1,8
Ratio weight/cake volume	23,8	11,8	8,9
<i>Weight ratio</i>			
GH+Glycine	0,651	0,560	0,555
Mannitol	1,650	1,140	1,140
(GH+Glycine):Mannitol	0.394	0,49	0.486
<i>Cake observation</i>			
	Good	Blow out	Blow out

The result was, that the lower the volume the better the cake appearance. The conclusion was that for small growth hormone amounts the weight/cake volume ratio has to be raised by lowering the filling volume. Raising by increasing the mannitol amount is not successful.

These results were confirmed in two more experiments, see table below.

Formulation	I	K
<i>First chamber, mg/cylinder</i>		
GH	0,35	1,06
Glycine	0,23	0,23
Mannitol	1,14	1,14
Sodium Phosphate	0,05	0,05
Disodium phosphate	0,03	0,03
Cake volume, ml	0,1	0,15
Weight of dry substances, mg	1,8	2,5
Ratio weight/cake volume	18,0	16,7
<i>Weight ratio</i>		
GH+Glycine	0,586	1,288
Mannitol	1,140	1,140
(GH+Glycine): Mannitol	0,567	1,129
<i>Cake observation</i>	Good	Good

Conclusion:

- 5 The observation that the cake volume should be lowered in order to increase the weight/cake volume ratio was confirmed. The lower the volume, the better the cake appearance. For small growth hormone amounts the weight/cake volume ratio thus has to be raised by lowering the filling volume. Raising by increasing the mannitol amount is not successful.
- 10 This is valid for formulations where the weight ratio between protein and amino acid versus stabilizer is less than 1.5.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common
 15 general knowledge in Australia.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. One-dose syringe comprising:
 - i) a first chamber with a freeze-dried composition comprising a protein in an amount of less than 1.4 mg, stabilizer and amino acid where the weight ratio between protein and amino acid versus stabilizer is less than 1.5 and in which the ratio of the weight of the dry component versus the cake volume is above 12 mg/ml; and
 - ii) a second chamber containing an aqueous reconstitution solution with an injectable volume of less than 0.5 ml.
2. Syringe according to claim 1 in which the ratio of the weight of the dry component versus the cake volume in the first chamber is above 15 mg/ml.
3. Syringe according to any one of the preceding claims in which the protein is growth hormone.
4. Syringe according to claim 3 wherein the growth hormone is human growth hormone.
5. Syringe according to any one of the preceding claims in which the amino acid is glycine.
6. Syringe according to claim 5 in which the amino acid is alanine.
7. Syringe according to any one of the preceding claims in which the stabilizer is mannitol.
8. Syringe according to any one of the preceding claims in which the first chamber comprises a buffer.
9. Syringe according to claim 8 wherein the buffer is sodium phosphate.



10. Syringe according to any one of the preceding claims in which the second chamber comprises an isotonic agent.
- 5 11. Syringe according to any one of the preceding claims in which the first chamber comprises mannitol and a buffer.
12. Syringe according to claim 11 wherein the buffer is sodium phosphate.
- 10 13. A syringe according to any one of claims 1 to 12 substantially as hereinbefore described with reference to the Examples.

DATED this 15th day of OCTOBER 2001

PHARMACIA & UPJOHN AB

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