

[0009] To increase toxin stability, stabilizing proteins such as human serum albumin (HSA) are often added in the art. Other stabilizing strategies involve the use of non-proteinaceous stabilizing agents, for example surfactants, polyvinylpyrrolidone (PVP), disaccharides, polyols and the like. In addition, it was disclosed in WO 00/15245 that a liquid formulation of highly concentrated botulinum toxin type B (about 2500 U/ml) is stable for up to 30 months when stored in glass vials at 5°C. However, this prolonged stability requires buffering the pH of the formulation down to an acidic pH of between 5 and 6, which causes pain upon injection. Other known approaches to increase toxin stability rely on the addition of various non-protein excipients which, however, are unsuitable or undesirable for human use (see, e.g., WO 01/58472, WO 2006/005910, and WO 2007/041664).

[0010] Thus, there is still no injectable botulinum toxin presentation available which is not only stable over a long period to provide a sufficiently long shelf life, but is also convenient and easy to use, reduces medication errors, and minimizes the risk of contamination.

OBJECTIVE OF THE INVENTION

[0011] In view of the above, the objective of the present invention is to provide a medical dosage form for the administration of botulinum toxin, which has a long shelf life and is convenient, safe and easy to use.

SUMMARY

[0012] The above object is solved by the provision of a botulinum toxin prefilled container (e.g., a syringe, vial, carpule, or ampoule) which is characterized by a superior long-term stability of the liquid botulinum toxin formulation in the container.

[0013] In one aspect, the present invention refers to a prefilled glass syringe comprising an aqueous botulinum toxin formulation, the glass syringe comprising (a) a syringe barrel made of glass including a proximal end and a distal end, and a generally cylindrical wall extending therebetween and defining a barrel lumen, the syringe barrel having a distally projecting tip with a fluid passage extending therethrough and communicating with the barrel lumen, wherein the generally cylindrical wall has an interior surface optionally coated with a barrier layer, (b) a capping device having an outlet engaging portion sealingly engaging and closing the distal open outlet end of the syringe, wherein the outlet engaging portion is made of an elastomeric material that optionally has a coating on its surface, and (c) a plunger rod assembly which extends into the proximal end of the syringe barrel and includes a plunger stopper in sliding fluid-tight engagement with the cylindrical wall of the barrel lumen, wherein the plunger stopper is made of an elastomeric material, which optionally has a coating on at least a portion of the plunger stopper that contacts the aqueous botulinum toxin formulation during storage and/or injection, wherein the elastomeric material of the outlet engaging

portion is selected from isoprene rubber (IS), butadiene rubber (BR), butyl rubber, halogenated butyl rubber, styrene-butadiene rubber, and mixtures thereof, and the elastomeric material of the plunger stopper is selected from isoprene rubber (IS), butadiene rubber (BR), butyl rubber, halogenated butyl rubbers, styrene-butadiene rubber, and mixtures thereof, and wherein the activity is not reduced by more than 25%, relative to the initial toxin activity, upon storage of the prefilled syringe for 12 months at 5°C or 12 months at 25°C. In one example, there is disclosed a prefilled glass container (e.g., a syringe, vial, carpule, or ampoule) comprising an aqueous botulinum toxin formulation, wherein the toxin activity is not reduced by more than 25%, preferably by not more than 20%, relative to the initial toxin activity, upon storage of the prefilled container (e.g., a syringe, vial, carpule, or ampoule) for (a) 12 months at 5°C, (b) 12 months at 25°C, or (c) 6 months at 30°C.

[0014] The stability of the aqueous botulinum toxin formulation in the prefilled container (e.g., a syringe, vial, carpule, or ampoule) in terms of the count of subvisible particles equal to or greater than 10 μm is also excellent and generally below 1000/ml during storage for 6 to 24 months (e.g., 6, 9, 12, 15, 18 or 24 months) at 2-30°C (e.g., at 5°C, 25°C or 30°C). Furthermore, the aqueous botulinum toxin formulation exhibits an excellent pH stability as indicated by a pH value that is generally not increased or decreased by more than 10%, relative to the initial pH value, during storage of the prefilled container (e.g., a syringe, vial, carpule, or ampoule) for 6 to 24 months (e.g., 6, 9, 12, 15, 18 or 24 months) at 2-30°C (e.g., at 5°C, 25°C or 30°C).

[0015] In another aspect, the present invention refers to a kit comprising a prefilled glass syringe as disclosed herein, and, optionally, instructions for use of said prefilled glass syringe. In one example, there is disclosed a kit comprising a prefilled glass container (e.g., a syringe, vial, carpule, or ampoule) according to one aspect of the invention and, optionally, instructions for use of said prefilled glass container.

[0016] In yet another example, there is disclosed a prefilled glass container (e.g., a syringe, vial, carpule, or ampoule) according to the first aspect of the present invention for use in therapy. For example, the prefilled glass container (e.g., a syringe, vial, carpule, or ampoule) may be used for treating a disease or condition caused by or associated with hyperactive cholinergic innervation of muscles or exocrine glands in a patient including, but not limited to, dystonia, spasticity, paratonia, diskinesia, focal spasm, strabismus, tremor, tics, migraine, sialorrhea and hyperhidrosis.

[0017] In still another aspect, the present invention refers to use of the prefilled glass syringe as disclosed herein for cosmetic applications, such as for treating wrinkles of the skin and facial asymmetries. In yet another example, there is disclosed the use of the

prefilled glass container (e.g., a syringe, vial, carpule, or ampoule) according to the first aspect of the invention for use in cosmetic treatments, such as for treating wrinkles of the skin and facial asymmetries, e.g. glabellar frown line, crow's feet, upper facial rhytides and platysma bands.

[0017A] In a further example, there is disclosed a use of an effective amount of botulinum toxin in the manufacture of a medicament for treating a disease or condition caused by or associated with hyperactive cholinergic innervation of muscles or exocrine glands in a patient, wherein the medicament is to be locally administered using the prefilled glass container as described herein.

[0018] In yet another example, there is disclosed a method for treating a disease or condition caused by or associated with hyperactive cholinergic innervation of muscles or exocrine glands in a patient, the method comprising locally administering an effective amount of botulinum toxin to a muscle or exocrine gland of the patient using the prefilled container (e.g., a syringe, vial, carpule, or ampoule) according to one aspect of the invention.

[0019] In a still further aspect, the present invention refers to a method for the cosmetic treatment of the skin, such as for treating wrinkles of the skin and facial asymmetries, the method comprising locally administering an effective amount of botulinum toxin to a patient by intradermal, subdermal or subcutaneous injection using the prefilled glass syringe as disclosed herein. In another example, there is disclosed a method for the cosmetic treatment of the skin, such as for treating wrinkles of the skin and facial asymmetries, the method comprising locally administering an effective amount of botulinum toxin to a patient by intradermal, subdermal or subcutaneous injection using the prefilled glass container (e.g., a syringe, vial, carpule, or ampoule) according to the first aspect of the present invention.

[0020] Further embodiments of the present invention are set forth in the appended dependent claims. The present invention may be more fully understood by reference

CLAIMS

1. A prefilled glass syringe comprising an aqueous botulinum toxin formulation, the glass syringe comprising
 - (a) a syringe barrel made of glass including a proximal end and a distal end, and a generally cylindrical wall extending therebetween and defining a barrel lumen, the syringe barrel having a distally projecting tip with a fluid passage extending therethrough and communicating with the barrel lumen, wherein the generally cylindrical wall has an interior surface optionally coated with a barrier layer,
 - (b) a capping device having an outlet engaging portion sealingly engaging and closing the distal open outlet end of the syringe, wherein the outlet engaging portion is made of an elastomeric material that optionally has a coating on its surface, and
 - (c) a plunger rod assembly which extends into the proximal end of the syringe barrel and includes a plunger stopper in sliding fluid-tight engagement with the cylindrical wall of the barrel lumen, wherein the plunger stopper is made of an elastomeric material, which optionally has a coating on at least a portion of the plunger stopper that contacts the aqueous botulinum toxin formulation during storage and/or injection,

wherein the elastomeric material of the outlet engaging portion is selected from isoprene rubber (IS), butadiene rubber (BR), butyl rubber, halogenated butyl rubber, styrene-butadiene rubber, and mixtures thereof, and

the elastomeric material of the plunger stopper is selected from isoprene rubber (IS), butadiene rubber (BR), butyl rubber, halogenated butyl rubbers, styrene-butadiene rubber, and mixtures thereof, and

wherein the activity is not reduced by more than 25%, relative to the initial toxin activity, upon storage of the prefilled syringe for 12 months at 5°C or 12 months at 25°C.

2. The prefilled glass syringe of claim 1, wherein the number of subvisible particles of equal to or greater than 10 μm is below 1000/ml during storage for 6 to 24 months at 2°C to 30°C.
3. The prefilled glass syringe of claim 1 or 2, wherein the pH value is not increased or decreased by more than 10%, relative to the initial pH value, upon storage of the prefilled syringe for 6 to 12 months at 5°C or 25°C or 30°C, or wherein the pH of the aqueous botulinum toxin formulation during storage is maintained in the range of 6.0 to 7.5, or both.
4. The prefilled glass syringe of any one of claims 1 to 3, wherein the botulinum toxin is present in the aqueous formulation at a concentration of 10 U/ml to 1000 U/ml.
5. The prefilled glass syringe of any one of claims 1 to 4, wherein the aqueous botulinum toxin formulation in the prefilled syringe does not contain a buffer.
6. The prefilled glass syringe of any one of claims 1 to 5, wherein the optional coating on the outlet engaging portion is a crosslinked silicone coating or a fluoropolymer coating.
7. The prefilled glass syringe of any one of claims 1 to 6, wherein the optional coating on the plunger stopper is a crosslinked silicone coating or a fluoropolymer coating.
8. The prefilled glass syringe of any one of claims 1 to 7, wherein the barrier layer of the syringe barrel is a silicone-free layer or a silicone layer.
9. A kit comprising a prefilled glass syringe according to any one of claims 1 to 8 and, optionally, instructions for use of said prefilled glass syringe.
10. Use of the prefilled glass syringe of any one of claims 1 to 8 for cosmetic applications, such as for treating wrinkles of the skin and facial asymmetries.

11. A method for the cosmetic treatment of the skin, such as for treating wrinkles of the skin and facial asymmetries, the method comprising locally administering an effective amount of botulinum toxin to a patient by intradermal, subdermal or subcutaneous injection using the prefilled glass syringe according to any one of claims 1 to 8.