

stability of liquid botulinum toxin formulations is still unsatisfactory and/or is achieved using undesirable substances for human use by injection (see, e.g., WO 01/58472, WO 2006/005910, and WO 2007/041664).

[0010] Furthermore, a liquid formulation of highly concentrated botulinum toxin type B (about 2500 U/ml) that is stable when stored in glass vials at 5°C for up to 30 months is disclosed in WO 00/15245. However, this stability is only achieved by using vials made of glass and buffering the pH of the solution down to an acidic pH of between 5 and 6, which causes pain upon injection.

[0011] Despite the advancements in the art, 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

[0012] In view of the above, the objective of the present invention is to provide a stable medical dosage form for the administration of botulinum toxin in a convenient, safe and simple manner.

SUMMARY

[0013] The above object is solved by the provision of a botulinum toxin prefilled plastic container (e.g., a syringe, vial, carpule or ampoule). The liquid botulinum toxin formulation in the prefilled plastic container (e.g., a syringe, vial, carpule or ampoule) is stable at 2-8°C over a prolonged period of time to provide a sufficiently long shelf life (at least about 12-24 months).

[0014] In one aspect, the present invention refers to A prefilled plastic syringe comprising an aqueous botulinum toxin formulation, the plastic syringe comprising (a) a plastic syringe barrel 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 contacting 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 rubber, styrene-butadiene rubber, and mixtures thereof, and wherein the biological activity of the botulinum toxin expressed in Mouse Units (MU) 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 3 months at 25°C. In one example, there is disclosed a prefilled plastic 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%, relative to the initial toxin activity, upon storage of the prefilled container for (a) 12 months at 5°C or (b) 3 months at 25°C.

[0015] 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 (number) of sub-visible 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 2-25°C (e.g., at 5°C or 25°C). Furthermore, the aqueous botulinum toxin formulation in the prefilled container 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 2-25°C (e.g., at 5°C or 25°C).

[0016] In another aspect, the present invention refers to a kit comprising a prefilled plastic syringe as disclosed herein and, optionally, instructions for use of said prefilled plastic syringe. In one example, there is disclosed a kit comprising a prefilled plastic container (e.g., a syringe, vial, carpule or ampoule) according to the first aspect of the invention and, optionally, instructions for use of said prefilled plastic container.

[0017] In yet another aspect, the present invention refers to a prefilled plastic syringe as disclosed herein for use in therapy. In one example, there is disclosed a prefilled plastic 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 plastic 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, dyskinesia, focal spasm, strabismus, tremor, tics, migraine, sialorrhea and hyperhidrosis.

[0018] In one aspect, the present invention refers to use of the prefilled plastic syringe of any one of claims 1 to 8 in cosmetic applications, such as for treating wrinkles of the skin and facial asymmetries. In another example, there is disclosed the use of the prefilled plastic container (e.g., a syringe, vial, carpule or ampoule) according to the first aspect of the

invention in cosmetic applications, such as for treating wrinkles of the skin and facial asymmetries, e.g. glabellar frown lines, crow's feet, upper facial rhytides and platysma bands.

[0019] In a yet further aspect, the present invention provides a method for the treatment of 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 by injection using the prefilled plastic container (e.g., a syringe, vial, carpule or ampoule) according to the first aspect of the invention.

[0019a] In yet a further aspect, the present invention provides use of an effective amount of botulinum toxin to a muscle or exocrine gland of the patient by injection using the prefilled plastic container as described herein, in the manufacture of a medicament for the treatment of a disease or condition caused by or associated with hyperactive cholinergic innervation of muscles or exocrine glands in a patient.

[0020] In another 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 plastic 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 plastic container (e.g., a syringe, vial, carpule or ampoule) according to the first aspect of the present invention.

[0021] Further embodiments of the present invention are set forth in the appended dependent claims. The present invention may be more fully understood by reference to the following detailed description of the invention, the examples and the accompanying drawings.

CLAIMS

1. A prefilled plastic syringe comprising an aqueous botulinum toxin formulation, the plastic syringe comprising
 - (a) a plastic syringe barrel 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 contacting 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 rubber, styrene-butadiene rubber, and mixtures thereof, and
wherein the biological activity of the botulinum toxin expressed in Mouse Units (MU) 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 3 months at 25°C.

2. The prefilled plastic syringe of claim 1, wherein the number of sub-visible particles of equal to or greater than 10 μm is below 1000/ml during storage for 6 to 24 months at 2°C to 25°C.
3. The prefilled plastic 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, during storage of the prefilled syringe for 6 to 24 months at 2°C to 25°C, or wherein the pH of the aqueous botulinum toxin formulation during storage is maintained in the range of 6.1 to 7.3, or both.
4. The prefilled plastic 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 plastic 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 plastic syringe of any one of claims 1 to 5, wherein the barrier layer of the syringe barrel is a silicone-free layer or a silicone layer.
7. The prefilled plastic syringe of any one of claims 1 to 6, wherein the optional coating on the outlet engaging portion is a crosslinked silicone coating or a fluoropolymer coating.
8. The prefilled plastic syringe of any one of claims 1 to 7, wherein the optional coating on the plunger stopper is a crosslinked silicone coating or a fluoropolymer coating.

9. A kit comprising a prefilled plastic syringe according to any one of claims 1 to 8 and, optionally, instructions for use of said prefilled plastic syringe.
10. A prefilled plastic syringe of any one of claims 1 to 8 for use in therapy.
11. Use of the prefilled plastic syringe of any one of claims 1 to 8 in cosmetic applications, such as for treating wrinkles of the skin and facial asymmetries.
12. Use of an effective amount of botulinum toxin to a muscle or exocrine gland of the patient by injection using the prefilled plastic syringe according to any one of claims 1 to 8, in the manufacture of a medicament for the treatment of a disease or condition caused by or associated with hyperactive cholinergic innervation of muscles or exocrine glands in a patient.
13. 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 plastic syringe according to any one of claims 1 to 8.