

CLAIMS

1. A botulinum toxin prefilled syringe system (10) comprising:

a syringe barrel (12) of glass, the syringe barrel (12) including an inner surface (20) defining a chamber (22) containing a liquid botulinum toxin formulation, having a proximal end (26) and a distal end (44), and having a label attached to its outside surface (40);

a plunger stopper (14) slidably positioned inside the syringe barrel (12) and providing a fluid-tight seal of the proximal end (26) of the syringe barrel (12);

a closure device (18) attached to the distal end (44) of the syringe barrel (12), the closure device (18) having an outlet engaging portion sealingly engaging and closing a distal open outlet end of the syringe system (10) to prevent leakage of the liquid botulinum toxin formulation;

characterized in that the plunger stopper (14) has a plurality of annular ribs (42a, 42b, 42c, 42d) providing multiple discrete contact areas with the inner surface (20) of the syringe barrel (12), and the botulinum toxin prefilled syringe system (10) has a normalized maximum gliding force of 20 N or less, as measured at a temperature of 20°C and using a 32Gx1/2" needle and a displacement speed of 100 mm/min, in which the normalized maximum gliding force is defined as follows:

$$GF_{\max} = GF_{\text{measured}} \times (d_{\text{barrel}})^2 / (D_{\text{barrel}})^2$$

in which:

$GF_{\max}$ is the normalized maximal gliding force in N,

GF_{measured} is the measured highest gliding force in N before the plunger stopper (14) finishes its course at the distal end of the syringe barrel (12),

d_{barrel} is the barrel inner diameter of a reference syringe and is 6.35 mm, and

D_{barrel} is the inner barrel diameter in mm of the prefilled syringe system (10),

in which the multiple discrete contact areas provide an independent seal with the inner surface (20) of the syringe barrel (12),

in which the annular ribs (42a, 42b, 42c, 42d) extend outward radially from an axis of the plunger stopper (14),

in which the annular rib (42a) located adjacent to the distal end (44) of the plunger stopper (14) has a greater Full Width at Half Maximum (FWHM) than the other annular ribs (42b, 42c, 42d) of the plunger stopper, in which the FWHM is herein defined as the width in the axial direction of the plunger stopper (14) between those two points on the surface of an annular rib (42a, 42b, 42c, 42d), which are half the maximum height in perpendicular direction to the axis of the plunger stopper, and

in which the distance between any two proximal adjacent annular ribs, except the most distal annular rib, in the axial direction of the plunger stopper is at least two times the sum of the full width at half maximum (FWHM) of the two adjacent annular ribs.

2. A botulinum toxin prefilled syringe system according to Claim 1, characterized in that the normalized break loose force is 15 N or less, and preferably lower than the maximum gliding force, as measured at a temperature of 20°C using a 32Gx1/2" needle and a displacement speed of 100 mm/min, in which the normalized break loose force is defined as follows:

$$BLF_{\text{norm}} = BLF_{\text{measured}} \times (d_{\text{barrel}})^2 / (D_{\text{barrel}})^2$$

in which:

BLF_{norm} is the normalized break loose force in N,

BLF_{measured} is the measured break loose force in N and is defined as the highest force between 0 and 2 mm plunger displacement distance,

d_{barrel} is the barrel inner diameter of a reference syringe and is 6.35 mm, and

D_{barrel} is the inner barrel diameter in mm of the prefilled syringe system (10).

3. A botulinum toxin prefilled syringe system according to Claim 1 or 2, characterized in that the normalized dynamic gliding force is 15 N or less, as measured at a temperature of 20°C using a 32Gx1/2" needle and a displacement speed of 100 mm/min, in which the normalized dynamic gliding force is defined as follows:

$$DGF_{\text{norm}} = DGF_{\text{measured}} \times (d_{\text{barrel}})^2 / (D_{\text{barrel}})^2$$

in which:

DGF_{norm} is the normalized dynamic gliding force in N,

DGF_{measured} is the mean gliding force calculated from the measured gliding forces at 1/3 and 2/3 of the total plunger displacement distance in N,

d_{barrel} is the barrel inner diameter of a reference syringe and is 6.35 mm, and

D_{barrel} is the inner barrel diameter in mm of the prefilled syringe system (10).

- 5 4. A botulinum toxin prefilled syringe system according to Claim 1, 2 or 3, in which (i) the normalized maximum gliding force (GF_{max}) is determined without storage or after storage for 12 months at 2 to 8°C or 25°C or (ii) the normalized break loose force (BLF_{norm}) is determined without storage or after storage for 12 months at 2 to 8°C or 25°C or (iii) the normalized dynamic gliding force (DGF_{norm}) is determined within storage or after storage for 12 months at 10 2 to 8°C or 25°C, or (iv) GF_{max} and BLF_{norm} , or GF_{max} and DGF_{norm} , or BLF_{norm} and DGF_{norm} , or GF_{max} , BLF_{norm} and DGF_{norm} are determined according to (i), (ii) or (iii).
5. A botulinum toxin prefilled syringe system according to any preceding claim, in which the number of annular ribs of the plunger stopper (14) is two to six, particularly two to five or three to four.
- 15 6. A botulinum toxin prefilled syringe system according to any preceding claim, characterized in that

(i) the plunger stopper (14) has a normalized total contact area with the inner surface (20) of the syringe barrel (12) of 70 mm² or less, in which the normalized total contact area is calculated as follows:

20
$$TCA_{\text{norm}} = TCA_{\text{calc}} \times (d_{\text{barrel}})^2 / (D_{\text{barrel}})^2$$

in which:

TCA_{norm} is the normalized total contact area in mm²,

TCA_{calc} is the calculated total contact area in mm² and is defined as the sum of the contact surfaces (CT_{rib}) of each annular rib (42a, 42b, 42c, 42d) in mm², in which CT_{rib} = $2\pi rh$, with r being the greatest distance perpendicular to the axis of the plunger stopper (14) between a point on the surface of the annular rib (42a, 42b, 42c, 42d) and the axis of the plunger stopper (14) in mm, and h being the full width at half maximum (FWHM) of the annular rib (42a, 42b, 42c, 42d) in mm, the FWHM being defined as the width in the axial direction of the plunger stopper (14) between those two points on the surface of the annular rib (42a, 42b, 42c, 42d) which are half the maximum height of the annular

rib (42a, 42b, 42c, 42d) in perpendicular direction to the axis of the plunger stopper (14),

d_{barrel} is the barrel inner diameter of a reference syringe and is 6.35 mm, and

D_{barrel} is the inner barrel diameter in mm of the prefilled syringe system (10), and/or

- 5 (ii) the percentage of the total contact area of the plunger stopper (14) with the inner surface (20) of the syringe barrel (12) to the total side face area of the plunger stopper (14) is 50% or less, in which the total side face area of the plunger stopper (14) is defined as follows:

$$\text{TSFA} = 2\pi r_{\text{max}} H$$

- 10 in which:

TSFA is the total side face area of the plunger stopper (14) in mm^2 ,

r_{max} being the greatest distance perpendicular to the axis of the plunger stopper (14) between a point on the surface of any annular rib (42a, 42b, 42c, 42d) and the axis of the plunger stopper (14) in mm, and

- 15 H is the total length of the plunger stopper (14) in axial direction in mm.

7. A botulinum toxin prefilled syringe system according to any preceding claim, characterized in that the inner surface (20) of the syringe barrel (12) is siliconized, particularly spray-siliconized or baked-on siliconized.

8. A botulinum toxin prefilled syringe system according to any preceding claim,
20 characterized in that the plunger stopper (14) is of an elastomeric material and optionally has a coating on at least a portion of the plunger stopper (14) such that the liquid botulinum toxin formulation contacts only the coating during storage and/or injection.

9. A botulinum toxin prefilled syringe system according to Claim 8, characterized in that

- (i) the elastomeric material is a synthetic rubber selected from the group consisting of
25 isoprene rubber, neoprene rubber, butadiene rubber, butyl rubber, styrene-butadiene copolymer, acrylonitrile-butadiene copolymer, polysulfide elastomers, urethane rubbers, and ethylene-propylene elastomers, and in which the elastomeric material is preferably a butyl rubber such as a halogenated butyl rubber, or

(ii) the coating on at least a portion of the plunger stopper (14) is a fluoropolymer coating, a crosslinked silicone coating, or a coating consisting of an outer crosslinked silicone coating layered on a fluoropolymer coating, or

(iii) the elastomeric material is defined as in (i) and the coating is defined as in (ii).

5 10. A botulinum toxin prefilled syringe system according to any preceding claim, characterized in that the outlet engaging portion of the closure device (18) is of an elastomeric material optionally having a coating on an outer surface thereof such that the liquid botulinum toxin formulation contacts only the coating during storage and/or injection.

11. A botulinum toxin prefilled syringe system according to Claim 10, characterized in that

10 (i) the elastomeric material is a synthetic rubber selected from the group consisting of isoprene rubber, neoprene rubber, butadiene rubber, butyl rubber, styrene-butadiene copolymer, acrylonitrile-butadiene copolymer, polysulfide elastomers, urethane rubbers, and ethylene-propylene elastomers, and in which the elastomeric material is preferably a styrene-butadiene copolymer, a butyl rubber or a butyl rubber-isoprene rubber blend,
15 and the butyl rubber being preferably a halogenated butyl rubber, or

(ii) the coating is a fluoropolymer coating, a crosslinked silicone coating, or a coating consisting of an outer crosslinked silicone coating layered on a fluoropolymer coating, or

(iii) the elastomeric material is defined as in (i) and the coating is defined as in (ii).

20 12. A botulinum toxin prefilled syringe system according to any preceding claim, in which the toxin activity is not reduced by more than 25%, relative to the initial toxin activity, upon storage of the prefilled container for 12 months at 5°C or 25°C.

13. A kit comprising a botulinum toxin prefilled syringe system according to any preceding claim and optionally instructions for use of the botulinum toxin prefilled syringe system (10).

25 14. Use of a botulinum toxin prefilled syringe system according to any of Claims 1 to 12 in cosmetic applications.