Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

VISTABEL, 4 Allergan Units/0.1ml, Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Botulinum toxin type A[1] .....4 Allergan Units per 0.1ml of reconstituted solution.
[1]of *Clostridium botulinum*

Allergan Units are not interchangeable with other preparations of botulinum toxin.

Vial of 50 Units
Vial of 100 Units

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
White Powder
VISTABEL product appears as a thin white deposit that may be difficult to see on the base of the vial.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VISTABEL is indicated for the temporary improvement in the appearance of:

- moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines) and/or,
- moderate to severe lateral canthal lines (crow's feet lines) seen at maximum smile and/or,
- moderate to severe forehead lines seen at maximum eyebrow elevation,

when the severity of the facial lines has an important psychological impact in adult patients.

4.2 Posology and method of administration

Posology
Refer to specific recommendations for each indication described below.

Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan Units are different from other botulinum toxin preparations.

Elderly patients
There is limited phase 3 clinical data with VISTABEL in patients older than 65 years (see section 5.1).
No specific dose adjustment is required for use in the elderly.

Paediatric population
The safety and effectiveness of VISTABEL in the treatment of glabellar lines seen at maximum frown, crow's feet lines seen at maximum smile, or forehead lines seen at maximum eyebrow elevation in individuals under 18 years of age have not been demonstrated.The use of VISTABEL is not recommended in individuals under 18 years (see section 4.4).

Method of Administration

VISTABEL should only be administered by physicians with appropriate qualifications and expertise in this treatment and use of the required equipment.

VISTABEL, after reconstitution, must be used only for one session of injection(s) per patient. The excess of unused product must be disposed of as detailed in section 6.6. Particular precautions should be taken for product preparation and administration as well as for the inactivation and disposal of the remaining unused solution (see section 4.4 and 6.6).

The recommended injection volume per muscle site is 0.1 ml. See also dilution table in section 6.6.

For instructions for use, handling and disposal of the vials, see section 6.6.

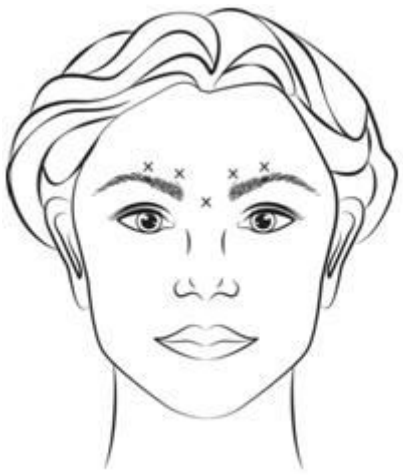
Care should be taken to ensure that VISTABEL is not injected into a blood vessel when it is injected in the vertical lines between the eyebrows seen at maximum frown (also known as glabellar lines), in the lateral canthal lines seen at maximum smile (also known as crow's feet lines), or in the forehead lines seen at maximum eyebrow elevation, see section 4.4.

Treatment intervals should not be more frequent than every three months.

Administration Instructions for Glabellar Lines seen at maximum frown:

Reconstituted VISTABEL (50 Units/1.25 ml or 100 Units/2.5 ml) is injected using a sterile 30 gauge needle. 0.1 ml (4 Units) is administered in each of the 5 injection sites (see Figure 1): 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 Units.

Before injection, the thumb or index finger is to be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection. In order to reduce the risk of eyelid ptosis,the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections in the corrugator muscle must be done in the central part of that muscle, a distance of at least 1 cm above the arch of the eyebrows.
Figure 1:



Improvement of severity of glabellar lines seen at maximum frown generally occurs within one week after treatment. The effect was demonstrated for up to 4 months after injection.

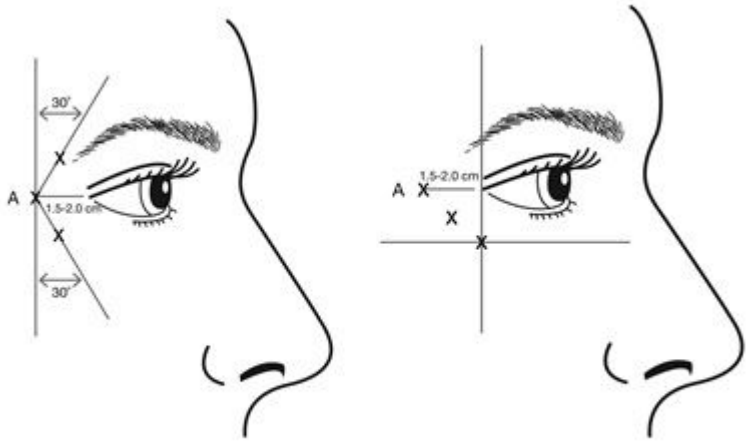
Administration Instructions for Crow's Feet Lines seen at maximum smile:

Reconstituted VISTABEL (50 Units/1.25 ml or 100 Units/2.5 ml) is injected using a sterile 30 gauge needle. 0.1 ml (4 Units) is administered in each of the 3 injection sites per side (total of 6 injection sites) in the lateral orbicularis oculi muscle, for a total dose of 24 Units in a total volume of 0.6 ml (12 Units per side).

In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections should be made temporal to the orbital rim, thereby maintaining a safe distance from the muscle controlling eyelid elevation.

Injections should be given with the needle tip bevel up and oriented away from the eye. The first injection (A) should be made approximately 1.5 to 2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow's feet region are above and below the lateral canthus, inject as shown in Figure 2. Alternatively, if the lines in the crow's feet region are primarily below the lateral canthus, inject as shown in Figure 3.

Figure 2: Figure 3:



For simultaneous treatment with glabellar lines seen at maximum frown, the dose is 24 Units for crow's feet lines seen at maximum smile and 20 Units for glabellar lines (see Administration Instructions for Glabellar Lines, and Figure 1), for a total dose of 44 Units in a total volume of 1.1 ml.

Improvement of severity of crow's feet lines seen at maximum smile, when assessed by the investigator, occurred within one week of treatment. The effect was demonstrated for a median of 4 months after injection.

Administration Instructions for Forehead Lines seen at maximum eyebrow elevation:

Reconstituted VISTABEL (50 Units/1.25 ml or 100 Units/2.5 ml) is injected using a sterile 30 gauge needle. 0.1 ml (4 Units) is administered in each of the 5 injection sites in the frontalis muscle, for a total dose of 20 Units in a total volume of 0.5 ml (see Figure 4).

The total dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units/1.0 mL.

To identify the location of the appropriate injection sites in the frontalis muscle, the overall relationship between the size of the subject's forehead, and the distribution of frontalis muscle activity should be assessed.

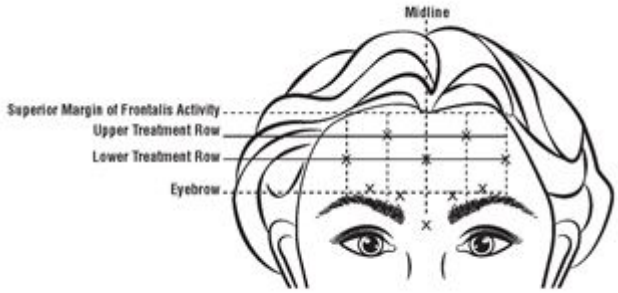
The following horizontal treatment rows should be located by light palpation of the forehead at rest and maximum eyebrow elevation:

• Superior Margin of Frontalis Activity: approximately 1 cm above the most superior forehead crease
• Lower Treatment Row: midway between the superior margin of frontalis activity and the eyebrow, at least 2 cm above the eyebrow
• Upper Treatment Row: midway between the superior margin of frontalis activity and lower treatment row

The 5 injections should be placed at the intersection of the horizontal treatment rows with the following vertical landmarks:

• On the lower treatment row at the midline of the face, and 0.5 – 1.5 cm medial to the palpated temporal fusion line (temporal crest); repeat for the other side.
• On the upper treatment row, midway between the lateral and medial sites on the lower treatment row; repeat for the other side.

Figure 4:



Improvement of severity of forehead lines seen at maximum eyebrow elevation occurred within one week of treatment. The effect was demonstrated for approximately 4 months after injection.

For simultaneous treatment with glabellar lines and crow's feet lines, the total dose is 64 Units, comprised of 20 Units for forehead lines, 20 Units for glabellar lines (see Administration Instructions for Glabellar Lines, and Figure 1), and 24 Units for crow's feet lines (see Crows Feet Lines Administration, and Figures 2 and 3).

General information

In case of treatment failure after the first treatment session, i.e. in the absence, at one month after injection, of significant improvement from baseline, the following approaches may be considered:
• Analysis of the causes of failure, e.g. incorrect muscles injected, injection technique, formation of toxin-neutralising antibodies**,** insufficient dose;
• Re-evaluation of the relevance of treatment with botulinum toxin type A;

In the absence of any undesirable effects secondary to the first treatment session, initiate a second treatment session with at least a three-month interval between the two treatment sessions.

For glabellar lines seen at maximum frown, in case of insufficient dose, initiate a second treatment session by adjusting the total dose up to 40 or 50 Units, taking into account the analysis of the previous treatment failure.

The efficacy and safety of repeat injections of VISTABEL beyond 12 months has not been evaluated.

4.3 Contraindications

VISTABEL is contraindicated,

- In individuals with a known hypersensitivity to botulinum toxin type A or to any of the excipients of the formulation;
- In the presence of myasthenia gravis or Eaton Lambert Syndrome;
- In the presence of infection at the proposed injection sites.

4.4 Special warnings and precautions for use

Particular precautions should be taken for product preparation and administration as well as for the inactivation and disposal of the remaining unused solution (see sections 4.2 and 6.6).

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium free”.

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering VISTABEL and injection into vulnerable anatomic structures must be avoided.

The recommended dosage and frequency of administration of VISTABEL should not be exceeded.

An anaphylactic reaction may occur very rarelyafter injection of botulinum toxin. Epinephrine (adrenaline) or any other anti-anaphylactic measures should therefore be available.

Patients with unrecognised neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of botulinum toxin type A. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube (see section 4.3).

Caution should also be exercised when VISTABEL is used for treatment of patients with amyotrophic lateral sclerosis or with peripheral neuromuscular disorders.

Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin (see section 4.8). Patients treated with therapeutic doses may experience exaggerated muscle weakness. Swallowing and breathing difficulties are serious and can result in death. Injection of VISTABEL is not recommended in patients with a history of dysphagia and aspiration.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Too frequent or excessive dosing may enhance the risk of antibody formation. Antibody formation may lead to treatment failure of botulinum toxin type A even for other indications.

As is expected for any injection procedure, localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection.
Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.
Caution should be taken when VISTABEL is used in the presence of inflammation at the proposed injection site(s) or when the targeted muscle shows excessive weakness or atrophy.
Care should be taken to ensure that VISTABEL is not injected into a blood vessel when it is injected in the glabellar lines seen at maximum frown, in the crow's feet lines seen at maximum smile, or in the forehead lines seen at maximum eyebrow elevation, see section 4.2.
There is a risk of eyelid ptosis following treatment, refer to Section 4.2 for administration instructions on how to minimise this risk.
The use of VISTABEL is not recommended in individuals under 18 years.There is limited phase 3 clinical data with VISTABEL in patients older than 65 years.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

Theoretically, the effect of botulinum toxin may be potentiated by aminoglycoside antibiotics,spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents).

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

No specific tests have been carried out to establish the possibility of clinical interaction with other medicinal products. No other interactions of clinical significance have been reported in this indication.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. VISTABEL is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

There is no information on whether VISTABEL is excreted in human milk. The use of VISTABEL during breastfeeding cannot be recommended.

Fertility
There are no adequate data on the effects on fertility from the use of botulinum toxin type A in women of childbearing potential. Studies in male and female rats have shown fertility reductions (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, VISTABEL may cause asthenia, muscle weakness, dizziness and visual disturbance, which could affect driving and the operation of machinery.

4.8 Undesirable effects

1. **General** In controlled clinical trials for glabellar lines seen at maximum frown, adverse events considered by the investigators to be related to VISTABEL were reported in 23.5% (placebo: 19.2%) of patients. In treatment cycle 1 of the pivotal controlled clinical trials for crow's feet lines seen at maximum smile, such events were reported in 7.6% (24 Units for crow's feet lines alone) and 6.2% (44 Units: 24 Units for crow's feet lines administered simultaneously with 20 Units for glabellar lines) of patients compared to 4.5% for placebo. In treatment cycle 1 of clinical trials for forehead lines seen at maximum eyebrow elevation, adverse events considered by the investigators to be related to VISTABEL were reported in 20.6% of patients treated with 40 Units (20 Units to the frontalis with 20 Units to the glabellar complex), and 14.3% of patients treated with 64 Units (20 Units to the frontalis with 20 Units to the glabellar complex and 24 Units to the lateral canthal lines areas), compared to 8.9% of patients that received placebo. Adverse reactions may be related to treatment, injection technique or both. In general, adverse reactions occur within the first few days following injection and are transient. Most adverse events reported were of mild to moderate severity. The expected pharmacological action of botulinum toxin is a local muscle weakness. However, weakness of adjacent muscles and/or muscles remote from the site of injection has been reported. Blepharoptosis**,** which may be technique-related**,** is consistent with the pharmacological action of VISTABEL. As is expected for any injection procedure, pain/burning/stinging, oedema and/or bruising may be observed in association with the injection. Fever and flu syndrome have also been reported after injections of botulinum toxin. **b) Adverse reactions - frequency** The adverse reactions are classified by System Organ Class and frequency defined as follows: Very Common (≥ 1/10); Common (≥ 1/100, <1/10); Uncommon (≥ 1/1,000, <1/100); Rare (≥ 1/10,000, <1/1,000); Very Rare (<1/10,000). *Glabellar Lines* The following adverse drug reactions were reported in the double-blind, placebo-controlled clinical studies following injection of VISTABEL 20 Units for glabellar lines alone:

System Organ Class	Preferred Term	Frequency
Infections and infestations	Infection	Uncommon
Psychiatric disorders	Anxiety	Uncommon
Nervous system disorders	Headache, paraesthesia	Common
	Dizziness	Uncommon
Eye disorders	Eyelid ptosis	Common
	Blepharitis, eye pain, visual disturbance (includes vision blurred)	Uncommon
Gastrointestinal disorders	Nausea	Common
	Oral dryness	Uncommon
Skin and subcutaneous tissue disorders	Erythema, skin tightness	Common
	Oedema (face, eyelid, periorbital), photosensitivity reaction, pruritus, dry skin	Uncommon
Musculoskeletal and connective tissue disorders	Localised muscle weakness	Common
	Muscle twitching, Mephisto sign (lateral elevation of eyebrows)	Uncommon
General disorders and administration site conditions	Face pain, injection site oedema, ecchymosis, injection site pain, injection site irritation	Common
	Flu syndrome, asthenia, fever	Uncommon

Crow's Feet Lines with or without Glabellar Lines

-

The following adverse drug reactions were reported in the double-blind, placebo-controlled clinical studies following injection of VISTABEL for crow's feet lines with or without glabellar lines:

System Organ class	Preferred Term	Frequency
Eye disorders	Eyelid oedema	Uncommon
General disorders and administration site conditions	Injection site haematoma*	Common
	Injection site haemorrhage*	Uncommon
	Injection site pain*	Uncommon
	Injection site paraesthesia	Uncommon

**procedure-related adverse reactions*

Forehead Lines and Glabellar Lines with or without Crow's Feet Lines

The following adverse drug reactions were reported in double-blind, placebo-controlled clinical studies following injection of VISTABEL for simultaneous treatment of forehead lines and glabellar lines with or without crow's feet lines:

System Organ Class	Preferred Term	Frequency
Nervous System Disorders	Headache	Common
Eye Disorders	Eyelid Ptosis[1]	Common
Skin and subcutaneous tissue disorders	Skin tightness	Common
	Brow Ptosis[2]	Common
Musculoskeletal and connective tissue disorders	Mephisto sign (lateral elevation of eyebrows)	Common
General disorders and administration site conditions	Injection site bruising*	Common
	Injection site haematoma*	Common
	Injection site pain*	Uncommon

[1]*The median time to onset of eyelid ptosis was 9 days following treatment*
[2]*The median time to onset of brow ptosis was 5 days following treatment*
******procedure-related adverse reactions*

No change was observed in the overall safety profile following repeat dosing.

c) Post-Marketing data (frequency not known)

The following adverse reactions or medically relevant adverse events have been reported since the drug has been marketed for the treatment of glabellar lines, crow's feet lines and other clinical indications:

System Organ Class	Preferred Term
Immune system disorders	Anaphylaxis, angioedema, serum sickness, urticaria
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Brachial plexopathy, dysphonia, dysarthria, facial paresis, hypoaesthesia, muscle weakness, myasthenia gravis, peripheral neuropathy, paraesthesia, radiculopathy, syncope, facial palsy
Eye disorders	Angle-closure glaucoma (for treatment of blepharospasm), eyelid ptosis, lagophthalmos, strabismus, vision blurred, visual disturbance, dry eye, eyelid oedema
Ear and labyrinth disorders	Hypoacusis, tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders	Aspiration pneumonia, dyspnoea, bronchospasm, respiratory depression, respiratory failure
Gastrointestinal disorders	Abdominal pain, diarrhoea, dry mouth, dysphagia, nausea, vomiting
Skin and subcutaneous tissue disorders	Alopecia, brow ptosis, dermatitis psoriasiform, erythema multiforme, hyperhidrosis, madarosis, pruritus, rash
Musculoskeletal and connective tissue disorders	Muscle atrophy, myalgia, localised muscle twitching/involuntary muscle contractions
General disorders and administration site conditions	Denervation atrophy, malaise, pyrexia

Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin (e.g. muscle weakness, dysphagia, constipation or aspiration pneumonia which can be fatal) (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Overdose of VISTABEL is a relative term and depends upon dose, site of injection, and underlying tissue properties. No cases of systemic toxicity resulting from accidental injection of botulinum toxin type A have been observed. Excessive doses may produce local, or distant, generalised and profound neuromuscular paralysis. No cases of ingestion of botulinum toxin type A have been reported.

Signs of overdose are not apparent immediately post-injection. Should accidental injection or ingestion occur, the patient should be medically supervised for several days for signs and symptoms of general weakness or muscle paralysis. Admission to hospital should be considered in patients presenting with symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:Muscle relaxants, peripherally acting agents,
ATC code: M03A X01.

Botulinum toxin type A *(Clostridium botulinum* neurotoxin) blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals by cleaving SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within the nerve endings leading to denervation of the muscle and therefore to a paralysis.

After injection, there is an initial rapid high-affinity binding of toxin to specific cell surface receptors. This is followed by transfer of the toxin across the plasma membrane by receptor-mediated endocytosis. Finally, the toxin is released into the cytosol. This latter process is accompanied by progressive inhibition of acetylcholine release, clinical signs are manifest within 2-3 days, with peak effect seen within 5-6 weeks of injection.

Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

Clinical data:

Glabellar Lines
537 patients with moderate to severe glabellar lines seen at maximum frown have been included in clinical studies.

VISTABEL injections significantly reduced the severity of glabellar lines seen at maximum frown for up to 4 months, as measured by the investigator assessment of glabellar line severity at maximum frown and by subject's global assessment of change in appearance of his/her glabellar lines seen at maximum frown. None of the clinical endpoints included an objective evaluation of the psychological impact. Thirty days after injection 80% (325/405) of VISTABEL-treated patients were considered by investigators as treatment responders (none or mild severity at maximum frown), compared to 3% (4/132) of placebo-treated patients. At this same timepoint, 89% (362/405) of VISTABEL-treated patients felt they had a moderate or better improvement, compared to 7% (9/132) of placebo-treated patients.
VISTABEL injections also significantly reduced the severity of glabellar lines at rest. Of the 537 patients enrolled, 39% (210/537) had moderate to severe glabellar lines at rest (15% had no lines at rest). Of these, 74% (119/161) of VISTABEL-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 20% (10/49) of placebo-treated patients.
There is limited phase 3 clinical data with VISTABEL in patients older than 65 years. Only 6.0% (32/537) of subjects were > 65 years old and efficacy results obtained were lower in this population.

Crow's Feet Lines

1362 patients with moderate to severe crow's feet lines seen at maximum smile, either alone (N=445, Study 191622-098) or also with moderate to severe glabellar lines seen at maximum frown (N=917, Study 191622-099), were enrolled.

VISTABEL injections significantly reduced the severity of crow's feet lines seen at maximum smile compared to placebo at all timepoints ($p < 0.001$) for up to 5 months. This was measured by the proportion of patients achieving a crow's feet lines severity rating of none or mild at maximum smile in both pivotal studies; until day 150 (end of study) in Study 191622-098 and day 120 (end of first treatment cycle in Study 191622-099). For both investigator and subject assessments, the proportion of subjects achieving none or mild crow's feet lines severity seen at maximum smile was greater in patients with moderate crow's feet lines seen at maximum smile at baseline, compared to patients with severe crow's feet lines seen at maximum smile at baseline. Table 1 summarises results at day 30, the timepoint of the primary efficacy endpoint.

In Study 191622-104 (extension to Study 191622-099), 101 patients previously randomised to placebo were enrolled to receive their first treatment at the 44 Units dose.Patients treated with VISTABEL had a statistically significant benefit in the primary efficacy endpoint compared to placebo at day 30 following their first active treatment. The response rate was similar to the 44 Units group at day 30 following first treatment in Study 191622-099.A total of 123 patients received4 cycles of 44 Units VISTABEL for combined crow's feet and glabellar lines treatment.

Table 1. Day 30: Investigator and Patient Assessment of Crow's Feet Lines Seen at Maximum Smile - Responder Rates (% of Patients Achieving Crow's Feet Lines Severity Rating of None or Mild)

Clinical Study	Dose	VISTABEL	Placebo	VISTABEL	Placebo
		Investigator Assessment		Patient Assessment	
191622-098	24 Units (crow's feet lines)	66.7%* (148/222)	6.7% (15/223)	58.1%* (129/222)	5.4% (12/223)
191622-099	24 Units (crow's feet lines)	54.9%* (168/306)	3.3% (10/306)	45.8%* (140/306)	3.3% (10/306)
	44 Units (24 Units crow's feet lines; 20 Units glabellar lines)	59.0%* (180/305)	3.3% (10/306)	48.5%* (148/305)	3.3% (10/306)

*$p < 0.001$ (VISTABEL vs placebo)

Improvements from baseline in subject assessment of the appearance of crow's feet lines at maximum smile were seen for VISTABEL (24 Units and 44 Units) compared to placebo, at day 30 and at all timepoints following each treatment cycle in both pivotal studies ($p < 0.001$).

Treatment with VISTABEL 24 Units also significantly reduced the severity of crow's feet lines at rest. Of the 528 patients treated, 63% (330/528) had moderate to severe crow's feet lines at rest at baseline. Of these, 58% (192/330) of VISTABEL-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 11% (39/352) of placebo-treated patients.

Improvements insubjects' self-assessment of age and attractiveness were also seenfor VISTABEL (24 Units and 44 Units) compared to placebo using the Facial Line Outcomes (FLO-11) questionnaire at the primary timepoint of day 30 ($p < 0.001$) and at all subsequent timepoints in both pivotal studies.

In the pivotal studies, 3.9% (53/1362) of patients were older than 65 years of age. Patients in this age group had a treatment response as assessed by the investigator, of 36% (at day 30) for VISTABEL (24 Units and 44 Units). When analysed by age groups of ≤ 50 years and > 50 years, both populations demonstrated statistically significant improvements compared to placebo. Treatment response for VISTABEL 24 Units, as assessed by the investigator, was lower in the group of subjects > 50 years of age than those ≤ 50 years of age (42.0% and 71.2%, respectively).

Overall VISTABEL treatment response for crow's feet lines seen at maximum smile is lower (60%) than that observed with treatment for glabellar lines seen at maximum frown (80%).

916 patients (517 patients at 24 Units and 399 patients at 44 Units) treated with VISTABEL had specimens analysed for antibody formation. No patients developed the presence of neutralising antibodies.

Forehead Lines

822 patients with moderate to severe forehead lines and glabellar lines seen at maximum contraction, either alone (N=254, Study 191622-142) or also with moderate to severe crow's feet lines seen at maximum smile (N=568, Study 191622-143), were enrolled and included in the primary populations for analyses of all primary and secondary efficacy endpoints. In the clinical studies forehead lines were treated in conjugation with glabellar lines.

For both investigator and patient assessments, the proportion of patients achieving none or mild forehead lines seen at maximum eyebrow elevation following VISTABEL injections was greater than patients treated with placebo at day 30, the timepoint of the primary efficacy endpoint (Table 2). The proportions of patients achieving at least a 1-grade improvement in forehead line severity from baseline at rest, and achieving none or mild upper facial line severity at maximum contraction are also provided.

Table 2: Day 30: Investigator and Patient Assessment of Forehead Lines and Upper Facial Lines at Maximum Contraction and Rest

Clinical Study	**Endpoint**	**VISTABEL**	**Placebo**	**VISTABEL**	**Placebo**
		Investigator Assessment		**Patient Assessment**	
Study 191622-142 40 U (20 U forehead lines + 20 U glabellar lines)	Forehead Lines at Max Contraction[a]	94.8% (184/194)	1.7% (1/60)	87.6% (170/194)	0.0% (0/60)
		p < 0.0005		p < 0.0005	
	Forehead Lines at Rest[b]	86.2% (162/188)	22.4% (13/58)	89.7% (174/194)	10.2% (6/59)
		p < 0.0001		p < 0.0001	
Study 191622-143 40 U (20 U forehead lines + 20 U glabellar lines)	Forehead Lines at Max Contraction[a]	90.5% (201/222)	2.7% (3/111)	81.5% (181/222)	3.6% (4/111)
		p < 0.0005		p < 0.0005	
	Forehead Lines at Rest[b]	84.1% (185/220)	15.9% (17/107)	83.6% (184/220)	17.4% (19/109)
		p < 0.0001		p < 0.0001	
Study 191622-143 64 U (20 U forehead lines + 20 U glabellar lines + 24 U crow's feet lines)	Forehead Lines at Max Contraction[a]	93.6% (220/235)	2.7% (3/111)	88.9% (209/235)	3.6% (4/111)
		p < 0.0005		p < 0.0005	
	Upper Facial Lines at Max Contraction[c]	56.6% (133/235)	0.9% (1/111)	n/a	
		p < 0.0001			

[a] *Proportion of patients achieving none or mild FHL severity at maximum eyebrow elevation*
[b] *Proportion of patients with at least a 1-grade improvement from baseline of FHL severity at rest*
[c] *Proportion of responders defined as the same patient achieving none or mild in forehead lines, glabellar lines, and crow's feet lines for each facial region at maximum contraction*

VISTABEL injections significantly reduced the severity of forehead lines seen at maximum eyebrow elevation compared to placebo for up to 6 months ($p < 0.05$): This was measured by the proportion of patients achieving a forehead lines severity rating of none or mild at maximum eyebrow elevation in both pivotal studies; until day 150 in Study 191622-142 (21.6% with VISTABEL treatment compared to 0% treated with placebo) and day 180 in Study 191622-143 (6.8% with VISTABEL treatment compared to 0% treated with placebo).

When all 3 areas were treated simultaneously in Study 191622-143 (VISTABEL 64 U group), VISTABEL injections significantly reduced the severity of glabellar lines for up to 6 months (5.5% with VISTABEL treatment compared to 0% treated with placebo), lateral canthal lines for up to 6 months (3.4% with VISTABEL treatment compared to 0% treated with placebo) and forehead lines for up to 6 months (9.4% with VISTABEL treatment compared to 0% treated with placebo).

A total of 116 and 150 patients received 3 cycles over 1 year of VISTABEL 40 Units (20 Units forehead lines with 20 Units glabellar lines) and 64 Units (20 Units forehead lines, 20 Units glabellar lines, and 24 Units crow's feet lines), respectively. The response rate for forehead lines improvement was similar across all treatment cycles.

Using the FLO-11 Questionnaire, improvements in patient-reported perceptions of how bothered they were by their forehead lines, looking older than their actual age, and attractiveness were observed in a significantly ($p < 0.001$) greater proportion of patients on VISTABEL 40 Units (20 Units forehead lines with 20 Units glabellar lines) and 64 Units (20 Units forehead lines, 20 Units glabellar lines, and 24 U crow's feet lines) compared to placebo at the primary timepoint of day 30 in Studies 191622-142 and 191622-143.

Using the Facial Lines Satisfaction Questionnaire (FLSQ), 78.1% (150/192) of patients in Study 191622-142 and 62.7% (138/220) in Study 191622-143 reported improvements in appearance-related and emotional impacts (as defined by items pertaining to feeling older, negative self-esteem, looking tired, feeling unhappy, looking angry) with VISTABEL 40 Units (20 Units forehead lines with 20 Units glabellar lines) treatment compared to patients treated with placebo 19.0% (11/58) in Study 191622-142 and 18.9% (21/111) in Study 191622-143 at day 30 ($p < 0.0001$ in both studies).

On the same questionnaire, 90.2% (174/193) of patients in Study 191622-142 and 79.2% (175/221, 40 Units), or 86.4% (203/235, 64 Units) in Study 191622-143 reported they were "very satisfied"/ "mostly satisfied" with VISTABEL 40 Units or 64 Units compared to patients treated with placebo (1.7% [1/58], 3.6% [4/110] in Study 191622-142 and Study 191622-143, respectively), at the primary timepoint of day 60 using the FLSQ ($p < 0.0001$ in both studies).

In the pivotal studies, 3.7% (22/587) of patients were older than 65 years of age. Patients in this age group had a treatment response, as assessed by the investigator, of 86.7% (13/15) (at Day 30) for VISTABEL compared to 28.6% (2/7) for placebo. Responder rates in this VISTABEL-treated subgroup were similar to those in the overall population, but statistical significance was not reached and comparisons are difficult to make when compared to placebo due to the small number of patients.

5.2 Pharmacokinetic properties

a) General characteristics of the active substance:
Distribution studies in rats indicate slow muscular diffusion of ^{125}I-botulinum neurotoxin A complex in the gastrocnemius muscle after injection, followed by rapid systemic metabolism and urinary excretion. The amount of radiolabeled material in the muscle declined with a half-life of approximately 10 hours. At the injection site, the radioactivity was bound to large protein molecules, whereas in the plasma it was bound to small molecules, suggesting rapid systemic metabolism of the substrate. Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine. Toxin is probably metabolised by proteases and the molecular components recycled through normal metabolic pathways.
Classical absorption, distribution, biotransformation and elimination (ADME) studies on the active substance have not been performed due to the nature of this product.

b) Characteristics in patients:
It is believed that at therapeutic doses, low systemic distribution of VISTABEL occurs. Clinical studies using single fibre electromyographic techniques have shown increased electrophysiologic neuromuscular activity in muscles distant to the injection site, with no associated clinical signs or symptoms.

5.3 Preclinical safety data

In reproductive studies in mice, rats, and rabbits, embryo toxicity was observed with high doses (delayed ossification and reduced foetal bodyweight). No teratogenic effects were observed in these species. In rats adverse effects on male fertility and female estrous cycling and fertility occurred only at high doses.
Studies on acute toxicity, repeated dose toxicity, local tolerance, mutagenicity, antigenicity and blood compatibility did not show unusual adverse local or systemic effects at clinically relevant dose levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Sodium chloride

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3 Shelf life

3 years.
After reconstitution, immediate use of the solution is recommended; However, physicochemical stability for 24 hours between +2°C and 8°C has been demonstrated.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (Type I glass) fitted with a stopper (chlorobutyl rubber) and a seal (aluminium);
Vial of 50 Allergan Units of Botulinum toxin type A – pack of one or pack of two;
Vial of 100 Allergan Units of Botulinum toxin type A – pack of one or pack of two.

NOT ALL PACK SIZES MAY BE MARKETED

6.6 Special precautions for disposal and other handling

Reconstitution should be performed in accordance with good practices rules, particularly for the respect of asepsis. VISTABEL has to be reconstituted with sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection). As per the dilution table below, the requested amount of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) has to be drawn up into a syringe in order to obtain a reconstituted solution at a concentration of 4 Units/0.1 ml;

Vial size	Amount of solvent added (sterileunpreserved normal saline solution (0.9% sodium chloride solution for injection))	Resulting dose (Units per 0.1 ml)
50 Units	1.25 ml	4.0 Units
100 Units	2.5 ml	4.0 Units

The central part of the rubber cap has to be cleaned with alcohol.
To avoid VISTABEL denaturation, the solution is prepared by injecting the solvent slowly into the vial and by gently rotating the vial avoiding bubble formation. The vial has to be discarded if the vacuum does not pull the solvent into the vial. Once reconstituted, the solution should be visually inspected prior to use. Only clear, colourless to slightly yellow solution without particles should be used.
It is mandatory that VISTABEL is used for one single patient treatment only during a single session.

Procedure to follow for a safe disposal of vials, syringes and materials used:

Immediately after use, and prior to disposal, unused reconstituted VISTABEL solution in the vial and/or the syringe must be inactivated, with 2 ml of dilute sodium hypochlorite solution at 0.5% or 1% and should be disposed of in accordance with local requirements.

Used vials, syringes, and materials should not be emptied and must be discarded into appropriate containers and disposed of as a Medical Biohazardous Waste in accordance with local requirements.

Recommendations in the event of an accident when handling botulinum toxin.

In the event of an accident when handling the product, whether in the vacuum-dried state or reconstituted, the appropriate measures described below must be initiated immediately.
· The toxin is very sensitive to heat and certain chemical agents
· Any spillage must be wiped up: either with an absorbent material soaked in a solution of sodium hypochlorite (Javel solution) in the case of the vacuum-dried product, or with a dry absorbent material in the case of the reconstituted product.
· Contaminated surfaces must be cleaned with an absorbent material soaked in a solution of sodium hypochlorite (Javel solution) and then dried.
· If a vial is broken, carefully collect up the pieces of glass and wipe up the product as stated above, avoiding cutting the skin.
· If splashed, wash with a solution of sodium hypochlorite and then rinse thoroughly with plenty of water.
· If splashed into the eyes, rinse one's eyes thoroughly with plenty of water or with an eye wash solution.
· If the operator injures himself (cuts, pricks himself), proceed as above and take the appropriate medical steps according to the dose injected.

This instruction for use and handling, and disposal should be strictly followed.

7 MARKETING AUTHORISATION HOLDER

AbbVie Limited
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1824/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 25th April 2008
Date of Last Renewal: 20th February 2008

10 DATE OF REVISION OF THE TEXT

March 2023