ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Boey 1 400 units powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 400 units of trenibotulinumtoxinE produced in *Clostridium botulinum* cells.

After reconstitution, each 0.1 mL of reconstituted solution contains 140 units of trenibotulinumtoxinE.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

White to off-white colour powder, which may also appear as broken disc.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Boey is indicated for the temporary improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown (glabellar lines), when these have an important psychological impact in adult patients (see section 5.1).

4.2 Posology and method of administration

Boey should only be administered by physicians with the appropriate qualifications and expertise in the treatment of glabellar lines and the use of required equipment.

Posology

Due to its early onset of effect and short duration, Boey should be used occasionally.

The potency of this medicinal product is expressed in units; these units are not interchangeable with the units used to express the potency of other botulinum toxin products.

Retreatment with Boey at intervals more frequent than every 6 weeks has not been evaluated and should be determined by physician.

The efficacy and safety of more than 3 consecutive injections of Boey beyond 18 weeks have not been evaluated.

Administration of botulinum toxin A less than 30 days after Boey has not been evaluated (see section 5.1).

Special populations

Elderly patients
No specific dose adjustment is required for use in the elderly.

Paediatric population
The safety and efficacy of Boey in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Intramuscular use.

For instructions on reconstitution and preparation of the medicinal product before administration, handling and disposal of the vials, see section 6.6.

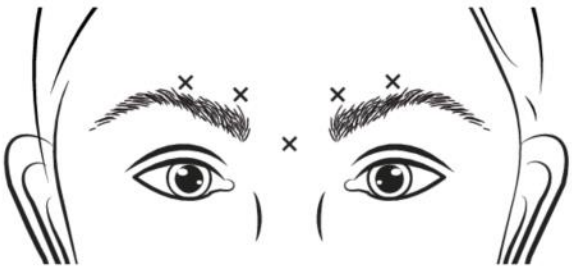
Preparation and reconstitution instructions
Prior to intramuscular injection, reconstitute each vial of Boey with 1 mL sodium chloride 9 mg/mL (0.9%) solution for injection, to obtain a reconstituted solution at a concentration of 140 units/0.1 mL and a total treatment dose of 700 units in 0.5 mL for glabellar lines.

Administration
Inject 140 units (0.1 mL) of reconstituted Boey intramuscularly into each of 5 sites, 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 700 units (see Figure 1).

In order to reduce the complication of ptosis, the following steps should be taken:

- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Position lateral corrugator muscle injections at least 1 cm above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate.

Figure 1. Injection sites for glabellar lines



Before re-injecting with Boey healthcare providers must ensure that the patient's glabellar lines are moderate to severe at maximum frown and confirm the absence of known adverse reactions to Boey.

4.3 Contraindications

- Hypersensitivity to the active substance, to any botulinum toxin preparation or to any of the excipients listed in section 6.1.
- Generalised disorders of muscle activity (e.g. Myasthenia gravis, Lambert-Eaton syndrome)
- Infection or inflammation at the proposed injection site(s).

4.4 Special warnings and precautions for use

Co-administration of Boey with another botulinum toxin at the same time has not been investigated and should be prohibited (see section 4.5).

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.

Hypersensitivity reactions

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

Distant spread of toxin effect

Botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms that are consistent with the mechanism of action of botulinum toxin may include muscular weakness, swallowing and speech disorders, aspiration pneumonia, difficulty breathing, and respiratory depression. Injection of this medicine is not recommended in patients with a history of dysphagia and aspiration.

Cases consistent with iatrogenic botulism have been reported following injection of other botulinum toxin products. Patients and caregivers should be advised to seek immediate medical care if they experience any signs or symptoms consistent with the spread of botulinum toxin effect or if swallowing, speech or respiratory disorders arise (see section 4.9).

Injection site pre-existing conditions and reactions

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering Boey.

Caution should be exercised when Boey is used in the presence of ptosis, or when excessive weakness or atrophy is present in the target muscle. Muscle atrophy is expected after repeated botulinum treatment secondary to the flaccid paralysis of the treated muscles.

Localised pain, inflammation, paraesthesia, hypoesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding, bruising, warmth, and/or induration have been associated with botulinum toxin injections. Needle-related pain and/or anxiety may result in vasovagal responses, including transient symptomatic hypotension and syncope.

Care should be taken to ensure that this medicinal product is not injected into a blood vessel when it is injected in the glabellar muscles.

Caution should be taken if complications have resulted with any previous botulinum toxin injections.

Repeated administrations

Repeated injections of trenibotulinumtoxinE may increase the risk of adverse reactions associated to the injection procedures.

Pre-existing neuromuscular disorders

Caution should also be exercised when Boey is used for treatment of patients with amyotrophic lateral sclerosis or with peripheral neuromuscular disorders. Patients with neuromuscular junction disorders (including unrecognised at the time of injection) may be at increased risk of clinically significant systemic effects, including severe dysphagia and respiratory compromise.

Ophthalmic adverse reactions in patients treated with other botulinum toxin products

Reduced blinking from injection with the use of other botulinum toxins has been reported which can lead to dry eye, corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve VII disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been conducted with Boey for injection.

Other botulinum neurotoxin products

The effect of administering different botulinum neurotoxin serotypes at the same time is unknown. Neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Muscle relaxants

Excessive weakness may be exaggerated by administration of a muscle relaxant before or after administration of botulinum toxins, including Boey.

Aminoglycosides and other medicinal products interfering with neuromuscular transmission

The effect of Boey may be potentiated by aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents).

Anticholinergic medicinal products

Use of anticholinergic medicinal products after administration of Boey, may potentiate systemic anticholinergic effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of trenibotulinumtoxinE in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

The use of Boey during pregnancy and in women of childbearing potential not using contraception is not recommended.

Breast-feeding

It is unknown whether Boey is excreted in human milk. A risk to the newborn/infant cannot be excluded.

The use of Boey during lactation is not recommended.

Fertility

There is no human or animal data with respect to fertility with trenibotulinumtoxinE. However, a botulinum toxin type A has been shown to impair the fertility of male and female animals only at dosages that induced exaggerated pharmacological effects.

4.7 Effects on ability to drive and use machines

Boey has minor influence on the ability to drive and use machines. There is a potential risk for eyelid ptosis and visual disturbance, which could affect driving and the operation of machinery.

4.8 Undesirable effects

Summary of the safety profile

The adverse drug reactions were eyelid ptosis, brow ptosis, and Mephisto sign (lateral elevation of eyebrow). These reactions were reported in 0.17%, 0.13%, and 0.04%, respectively, in subjects receiving Boey 700 units.

Tabulated list of adverse reactions

The frequency of adverse reactions is 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).

Table 1. Adverse drug reactions

System Organ Class	Adverse Drug Reaction	Frequency
Eye disorders	Eyelid ptosis	Uncommon
Skin and subcutaneous tissue disorders	Brow ptosis	Uncommon
Musculoskeletal and connective tissue disorders	Mephisto sign (lateral elevation of eyebrows)	Rare

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose may not be apparent immediately post-injection. Excessive doses may produce local, or distant, generalised and profound neuromuscular paralysis.

Should accidental injection or oral ingestion occur, or overdose or spread of toxin be suspected, medically monitor the patient for up to several weeks for progressive signs or symptoms of systemic muscular weakness or muscle paralysis which could be local to, or distant from, the site of injection, and may include ptosis, diplopia, dysphagia, dysarthria, generalised weakness or respiratory failure.

Consider these patients for further medical evaluation and immediately institute appropriate medical therapy, which may include hospitalisation.

If the musculature of the oropharynx and oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralysed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, other peripherally acting agents, ATC code: not yet assigned

Mechanism of action

TrenibotulinumtoxinE exerts its effect by blocking neuromuscular transmission. After intramuscular injection, the toxin undergoes rapid binding to specific cell surface receptors on motor nerve terminals. After binding, toxin is transported across the plasma membrane via receptor-mediated endocytosis and the proteolytic light chain is then released into the cytosol, where it acts by cleaving SNAP-25, a pre-synaptic protein involved in vesicle docking and fusion required for acetylcholine transmitter release. By disrupting SNAP-25, the toxin inhibits acetylcholine release from nerve terminals, resulting in partial chemical denervation and a localised reduction in muscle activity.

The clinical effects of Boey begin to manifest 8 hours post-injection with a peak around day 7 after injection. Recovery generally occurs within 2-3 weeks as primary nerve terminals recover.

A Phase 1, double-blind study was conducted with sequential administration of Boey 700 units or placebo on Day 1 followed by a botulinum toxin A 20 Allergan units (units are toxin-specific) on Day 30 in a total of 90 subjects with moderate to severe glabellar lines. The pharmacodynamic effect, as assessed using Facial Wrinkle Scale (FWS), was similar between treatment groups, regardless of whether the subject initially received Boey or placebo.

Immunogenicity

In five glabellar line studies, 2 104 subjects treated with Boey had samples analysed for antibody formation. Among Boey-treated subjects who received single or repeat treatments (up to three treatments), one subject (< 0.1%) developed binding antibodies. This subject received three treatments of Boey 700 units at 6-week interval and was negative for neutralising antibodies. This subject did not demonstrate cross-reactivity to botulinum toxin type A. Across all studies, no subject (0%) developed neutralising antibodies. Overall, anti-drug antibodies (ADA) were very rarely detected. There was no evidence of ADA impact on safety or efficacy, and risk of cross-reactivity to botulinum toxin type A is low; however, data are still limited.

Clinical efficacy and safety

A total of 725 adult subjects with moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity, who were psychologically impacted by their glabellar lines, were included in two randomised, multi-centre, double-blind, placebo-controlled studies of identical design (N=498, Study M21-500; N=227, Study M21-508). Adult subjects were enrolled on baseline Day 1 (Hour 0).

Subjects were eligible for treatment with Boey at the Day 43 Visit if retreatment criteria were met, including moderate to severe glabellar lines at maximum frown.

In these two studies, the majority of subjects were female. All races (White, Black, Asian, and others) and ethnicity (Hispanic and non-Hispanic) were included. Subjects were 20 to 81 years old, with a mean age of 46 years.

The primary efficacy instrument to assess glabellar line severity at maximum frown was the 4-point Facial Wrinkle Scale (FWS) (0=none, 1=mild, 2=moderate, 3=severe) used by both the investigator and subject. The investigator and subject assessments were performed independently.

The co-primary efficacy measure (treatment responder rate) was defined as the percentage of subjects achieving a ≥ 2-grade improvement from baseline in glabellar line severity at maximum frown at Day 7 based separately on investigator and subject assessments using FWS.

Both co-primary efficacy measures showed statistically significant improvements with the Boey group compared to placebo group for both studies M21-500 and M21-508, including all randomised subjects with baseline FLO-11 Total Transformed Score ≤ 50. Results are included below (Table 2).

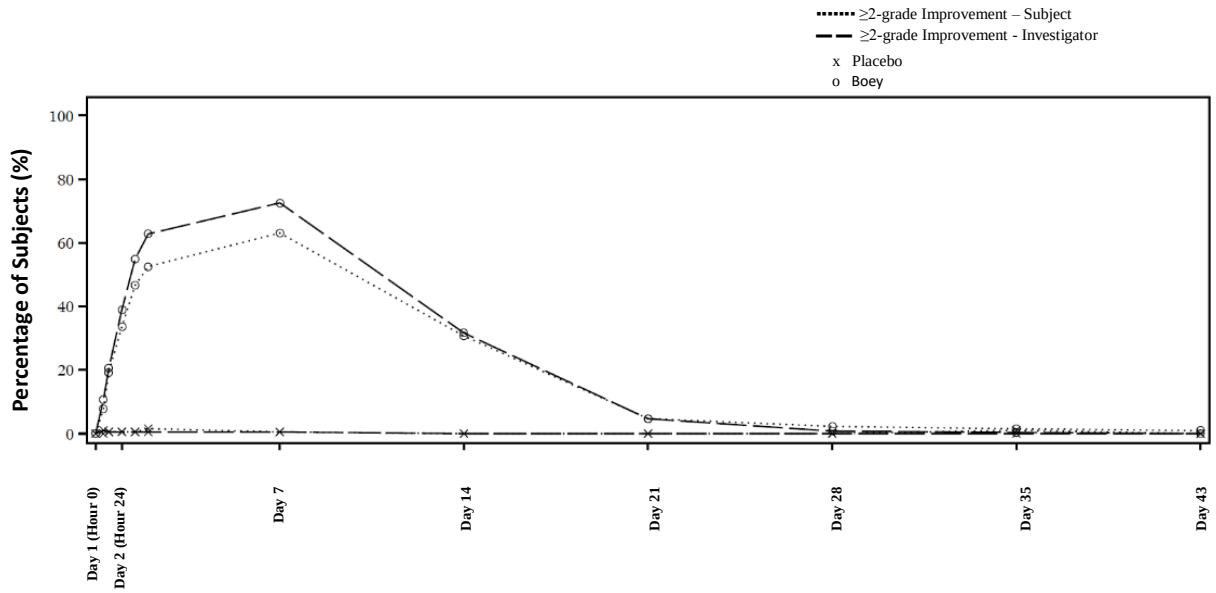
Table 2. Co-primary efficacy endpoints: Investigator and subject assessments of glabellar line severity at maximum frown – responder rates (% of subjects achieving ≥2-grade improvement from baseline at Day 7)

	Study M21-500		**Study M21-508**	
	Boey 700 units n (%) 95% CI	**Placebo n (%) 95% CI**	**Boey 700 units n (%) 95% CI**	**Placebo n (%) 95% CI**
ITT Population with Baseline FLO-11 Total Transformed Score ≤ 50	**(N=368)**	**(N=130)**	**(N=164)**	**(N=63)**
Investigator Assessment	265 (72.1%)* (67.5%, 76.7%)	1 (0.8%) (0.0%, 4.2%)	121 (73.6%)* (66.8%, 80.4%)	0 (0%) (0.0%, 5.7%)
Subject Assessment	224 (61.0%)* (55.9%, 66.0%)	1 (0.8%) (0.0%, 4.2%)	111 (67.9%)* (60.7%, 75.0%)	0 (0%) (0.0% 5.7%)

*p < 0.0001 (Boey vs placebo)

The percentages of subjects achieving ≥ 2-grade improvement from baseline over time are shown in Figure 2. Improvement in glabellar lines started within hours after injection. The peak effect was seen at Day 7 and duration of response lasted 2 to 3 weeks after Boey injection.

Figure 2. ≥2-grade improvement from baseline on the FWS according to subject and investigator assessments of glabellar lines severity at maximum frown over time (double-blind period) (Studies M21-500 and M21-508)



In M21-500 and M21-508 studies, most subjects (724/725) were younger than 80 years. Subjects in this age group had treatment responder rates, as assessed by the investigator, of 72.7% (386/531) for Boey and 0.5% (1/193) for placebo.

In the M21-500 and M21-508 studies, the secondary efficacy measures assessed psychological impact, ≥ 1-grade improvement in glabellar lines severity, overall treatment satisfaction, and satisfaction with natural look. The 11-item Facial Line Outcomes (FLO-11) questionnaire evaluates appearance-related psychological impacts due to glabellar lines including, how bothered they were by their glabellar lines, looking older than they want to look, feeling unattractive, looking older than their actual age, looking less attractive, looking not well rested, skin not looking smooth, looking tired, looking stressed, looking angry, and feeling good about facial appearance.

Using the FLO-11 total score, 66.6% of subjects in Study M21-500 and 61.9% of subjects in M21-508 study reported improvements in appearance-related psychological impacts with Boey compared to subjects treated with placebo (8.5% and 7.9%, respectively) at Day 7, as assessed by a ≥ 20-point change from baseline ($p < 0.0001$ in both studies).

Using the Facial Lines Satisfaction Questionnaire (FLSQ), overall satisfaction with treatment effect (Item 5), more subjects in M21-500 and M21-508 studies, 58.7% and 68.5%, respectively, reported being *Mostly satisfied* or *Very satisfied* with Boey treatment compared to subjects treated with placebo (16.2% and 9.9%, respectively) at Hour 24 ($p < 0.0001$ in both studies).

Using satisfaction with achieving a natural look (FLSQ Item 4), more subjects in M21-500 and M21-508 studies, 77.7% and 86.0%, respectively, reported being *Mostly satisfied* or *Very satisfied* with Boey treatment compared to subjects treated with placebo (7.7% and 7.9%, respectively) at Day 7 ($p < 0.0001$ in both studies).

Boey also reduced the severity of glabellar lines at rest. In the M21-500 and M21-508 studies, 53.0% and 49.4% had moderate to severe glabellar lines at rest at baseline as assessed by subject and investigator, respectively. Of these, 64.6% and 63.2% of Boey-treated subjects were responders at rest

with none or mild severity on Day 7, compared with 8.1% and 10.0% of placebo-treated subjects as assessed by subject and investigator, respectively.

The response rate for glabellar lines improvement was similar across all treatment cycles.

There are limited phase 3 clinical data with Boey in patients older than 65 years. Only 7% (38/532) of subjects were ≥65 years old and treatment responder rates at Day 7 were lower in this population (58% according to investigator and 37% according to subject).

5.2 Pharmacokinetic properties

General characteristics of the active substance

Using currently available analytical technologies, it is not possible to detect trenibotulinumtoxinE in peripheral blood after intramuscular injection at the recommended dose.

5.3 Preclinical safety data

Studies in animals have not been conducted to evaluate the carcinogenicity and mutagenicity. Nonclinical toxicology data did not reveal specific hazard for humans based on acute and chronic studies. In studies in mice, a reduction of tidal volume and an increase in minute volume were observed at supraclinical doses. Conventional developmental and reproduction toxicity studies were not conducted with Boey.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Poloxamer 188
L-methionine
L-histidine
L-histidine hydrochloride monohydrate
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

Unopened vial

3 years

Reconstituted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C.
From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not normally be longer than 24 hours at 2 °C – 8 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Keep the vial in the original carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial fitted with a stopper (chlorobutyl rubber) and a seal (aluminium).

Each pack contains one vial.

6.6 Special precautions for disposal and other handling

Procedure to follow for reconstitution

Reconstitute Boey only with sterile unpreserved 0.9% sodium chloride solution for injection. Draw up an appropriate amount of diluent into a syringe (see Table 3).

Table 3 Dilution table

Diluent added (sodium chloride 9 mg/mL (0.9%) solution for injection)	Resulting dose (units per 0.1 mL)
1 mL	140

Allow the vacuum to draw the sodium chloride solution from the syringe into the vial, letting it slowly and gently drip down the vial wall. Discard the vial if there is evidence of a loss of vacuum (i.e., if diluent is not pulled into the vial upon insertion of the needle). Reconstituted Boey is a clear colourless to slightly yellow solution. The reconstituted solution should be visually inspected for clarity and absence of particles prior to use. Do not inject reconstituted Boey if particulates are visible.

This medicinal product is for single use only and any unused solution should be discarded.

Procedure to follow for injecting syringe preparation

To achieve a 0.5 mL volume delivery, an adequate amount of reconstituted solution must be drawn into the syringe to account for volume loss from air bubble removal and syringe/needle priming.

- Draw more than 0.5 mL of the reconstituted solution into a sterile syringe and expel any air bubbles.
- Remove the needle used to withdraw the product. Attach an appropriately sized needle for injection and prime the needle.

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

All vials (including expired vials), syringes, or materials used in direct contact with the active substance should be disposed of as medical waste. In cases when deactivation of the toxin is desired (e.g., spills), the use of sodium hypochlorite (NaClO) at not less than 0.7% or household bleach solution at not less than 10% volume/volume for 10 minutes is recommended prior to disposal as medical waste.

Recommendations in the event of an accident when handling botulinum toxin

In the event of an accident when the product is being handled, whether in the powder state or reconstituted, the appropriate measures described below must be initiated immediately.

- Any spillage must be wiped up: either with an absorbent material soaked in a solution of sodium hypochlorite in the case of the powder 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 and then dried.
- If a vial is broken, proceed as stated above, carefully collect up the pieces of glass, avoiding cutting the skin, and wipe up the product.
- If splashed onto the skin, wash with a solution of sodium hypochlorite and then rinse thoroughly with plenty of water.
- If splashed into the eyes, flush thoroughly with plenty of water or with an eye wash solution.
- If injured oneself (cuts, pricks oneself), proceed as above and take the appropriate medical steps according to the dose injected.

7. MARKETING AUTHORISATION HOLDER

AbbVie Limited
70 Sir John Rogerson's Quay
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2044/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Allergan Sales, LLC
2525 Dupont Drive
Irvine, California 92612
United States of America

Name and address of the manufacturer responsible for batch release

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen Am Rhein, Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Boey 1 400 units powder for solution for injection
trenibotulinumtoxinE

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 1 400 units of trenibotulinumtoxinE.
After reconstitution, each 0.1 mL of solution contains 140 units of trenibotulinumtoxinE.
Units are not interchangeable with other preparations of botulinum toxin products.

3. LIST OF EXCIPIENTS

Excipients: Trehalose dihydrate, Poloxamer 188, L-methionine, L-histidine, L-histidine hydrochloride monohydrate, sodium chloride.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after reconstitution.
For single use only.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Limited
70 Sir John Rogerson's Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2044/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Boey 1 400 units powder for injection
trenibotulinumtoxinE
IM after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 400 units

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Boey 1 400 units powder for solution for injection
trenibotulinumtoxinE

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Boey is and what it is used for

Boey contains the active substance trenibotulinumtoxinE.

It belongs to a group of medicines that work as muscle relaxants. It temporarily prevents muscles near the injection site from moving.

Boey is used for the temporary improvement in the appearance of vertical lines between the eyebrows (glabellar lines) seen at maximum frown in adults for whom those lines have an important psychological impact.

2. What you need to know before you are given Boey

You should not be given Boey
- if you are allergic to trenibotulinumtoxinE or any of the other ingredients of this medicine (listed in section 6)
- if you have any long-term diseases affecting the muscles, such as myasthenia gravis or Lambert-Eaton syndrome
- if you have redness or swelling (inflammation) or an infection in the area(s) where the medicine is planned to be injected

Warnings and precautions

Your doctor should not give you Boey with another botulinum toxin. Using these medicines at the same time has not been studied.

Talk to your doctor before being given Boey if:
- you had a side effect from any botulinum toxin product in the past
- you have had facial surgery or injured your face

- you are planning to have facial surgery soon
- your muscles where the injection will be given are weak
- you have drooping of one or both eyelids (ptosis)
- you have certain diseases that affect your nervous system (such as amyotrophic lateral sclerosis or motor neuropathy)
- you have a history of trouble swallowing (dysphagia)
- you have a history of unwanted food or liquid going into the airways (aspiration)

Injection site reactions: reactions at the injection site may happen after receiving Boey, including the following:
- Pain/discomfort
- Decreased feeling to touch, pain, or hot and cold
- Numbness, tingling, pins and needles
- Swelling/inflammation
- Infection
- Redness
- Bruising
- Bleeding
- Itching
- Warmth
- Hardness at the site where the needle entered your skin

Your risk of having any of the above symptoms is higher the more treatments you get.

After you get Boey, tell your doctor if you have any of the following:
- **Allergic reaction**: An allergic reaction is a reaction your body has to a medicine. This can cause symptoms such as hives, rash, or fever. **Contact your doctor right away** if you have any of the symptoms listed below as they can be signs of a severe allergic reaction.
  - Trouble breathing, swallowing, or speaking
  - Swelling, including swelling of the face or throat
  - Wheezing (a whistling sound while breathing)
  - Feeling dizzy or light-headed
  - Shortness of breath

- **Distant spread of toxin effect**: Sometimes, the effects of botulinum toxin may spread from the injection area to other parts of the body. **Contact your doctor right away** if you have any of the symptoms listed below.
  - Muscle weakness
  - Trouble breathing, swallowing or speaking
  - Unwanted food or liquid going into the airways

- **Reduced blinking** in one or both eyes, which can lead to **dryness and damage to the outer layer of the eye.**

Children and adolescents
Boey is not recommended for patients younger than 18 years of age.

Other medicines and Boey
Tell your doctor if you are taking, have recently taken, or might take any medicines, including:
- A different medicine which contains botulinum toxins
- Muscle relaxants (medicines that reduce muscle tension)
- Aminoglycoside antibiotics (medicines used to treat infections) or other medicines that can affect how nerves communicate with muscles
- Anticholinergics (medicines that reduce muscle strength)

Ask your doctor for advice before you take any new medicines.

Pregnancy and breast-feeding
It is not recommended to use Boey if you are pregnant.

Tell your doctor if you are pregnant before your treatment, plan to get pregnant, or get pregnant after your treatment. Your doctor will talk with you about whether you should continue treatment.

It is not known if Boey passes into breast milk. Breast-feeding is not recommended during treatment with Boey.

Driving and using machines
Boey has minor influence on the ability to drive and use machines. If you have drooping eyelids or problems with your vision after using Boey, do not drive or use machinery until those symptoms go away. If you are not sure, ask your doctor or pharmacist for advice.

Boey contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How Boey is given

Boey should only be given by doctors with the appropriate qualifications and expertise in this treatment and use of the required equipment.

Boey is given as an injection into the muscles (intramuscularly), directly into the affected area above and between the eyebrows. The usual dose is 700 units in total. You will be injected with 140 units of Boey into each of the 5 injection sites (glabellar lines).

Boey may start working as soon as 8 hours after injection with the full effect by day 7 after injection and a short duration of effect (2-3 weeks). Boey should be used occasionally.

Your doctor will decide when you should receive additional injections by checking your glabellar lines and confirming you did not have any side effects to your earlier treatments with Boey.

If you receive more Boey than you should

Contact your doctor immediately if you notice symptoms that you might have received too much Boey. These symptoms may not happen for several days after the injection, and include:
- Muscle weakness. This can happen near or away from the injection site.
- Trouble breathing, swallowing, or speaking. This may happen because the muscle cannot move (muscle paralysis).
- Food or liquid accidentally going into your lungs because the muscle cannot move, which might cause infection of the lungs (aspiration pneumonia). This kind of pneumonia can cause coughing, trouble breathing, chest pain, and/or confusion.
- Drooping of the eyelids.
- Double vision (seeing two objects when there is only one).
- Overall weakness in the body.

If you swallow Boey or have it accidentally injected, see your doctor. They may want to watch you closely for several days.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects seen with Boey in clinical trials are listed below.

Uncommon: may affect up to 1 in 100 people
- Drooping (ptosis) eyelid
- Drooping (ptosis) eyebrow

Rare: may affect up to 1 in 1 000 people
- Raising of the outer eyebrow (Mephisto sign)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Boey

Your doctor is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and outer carton after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Keep the vial in the original carton in order to protect from light.

After mixing the powder with sodium chloride 9 mg/mL (0.9%) solution for injection, the medicine should be used immediately. However, it can be stored for up to 24 hours in a refrigerator (2 °C – 8 °C).

Do not use this medicine if you notice visible particulates.

This medicine is for single use only and any unused solution should be discarded.

Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.

6. Contents of the pack and other information

What Boey contains

- The active substance is trenibotulinumtoxinE. Each vial contains 1 400 units of trenibotulinumtoxinE.
- The other ingredients are trehalose dihydrate, Poloxamer 188, L-methionine, L-histidine, L-histidine hydrochloride monohydrate, sodium chloride.

What Boey looks like and contents of the pack

Boey is a powder for solution for injection (powder for injection). It is a white powder or broken disc that comes in a clear glass container (vial).

Each pack has 1 vial.

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Other sources of information

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Potency units for Boey are not interchangeable with other preparations of botulinum toxin products.

Preparation, reconstitution, and handling

Reconstitute Boey only with sterile unpreserved 0.9% sodium chloride solution for injection. Draw up an appropriate amount of diluent into a syringe (see below Table).

Dilution Table

Diluent added (sodium chloride 9 mg/mL (0.9%) solution for injection)	Resulting dose (units per 0.1 mL)
1 mL	140

Allow the vacuum to draw the sodium chloride solution from the syringe into the vial, letting it slowly and gently drip down the vial wall. Discard the vial if there is evidence of a loss of vacuum (i.e. if diluent is not pulled into the vial upon insertion of the needle). Reconstituted Boey is a clear, colourless to slightly yellow solution. The reconstituted solution should be visually inspected for clarity and absence of particles prior to use. Do not inject reconstituted Boey if particulates are visible.

To achieve a 0.5 mL volume delivery, an adequate amount of reconstituted solution must be drawn into the syringe to account for volume loss from air bubble removal and syringe/needle priming.

- Draw more than 0.5 mL reconstituted solution into the sterile syringe and expel any air bubbles.
- Remove the needle used to withdraw the product. Attach an appropriately sized needle for injection and prime the needle.

Store reconstituted Boey in a refrigerator (2 °C – 8 °C) and administer within 24 hours of reconstitution. This medicinal product is for single use only and any unused solution should be discarded.

Administration

Inject 140 units (0.1 mL) of reconstituted Boey intramuscularly into each of 5 sites, 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 700 units.

Overdose

Symptoms of overdose may not be apparent immediately post-injection. Excessive doses may produce local, or distant, generalised and profound neuromuscular paralysis.

Should accidental injection or oral ingestion occur, or overdose or spread of toxin be suspected, the patient should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness or muscle paralysis which could be local to, or distant from, the site of injection, and may include ptosis, diplopia, dysphagia, dysarthria, generalised weakness or respiratory failure.

Consider these patients for further medical evaluation and immediately institute appropriate medical therapy, which may include hospitalisation.

If the musculature of the oropharynx and oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralysed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

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

All vials (including expired vials), syringes, and/or materials used in direct contact with the active substance should be disposed of as medical waste. In cases when deactivation of the toxin is desired (e.g., spills), the use of sodium hypochlorite (NaClO) at not less than 0.7% or household bleach

solution at not less than 10% volume/volume for 10 minutes is recommended prior to disposal as medical waste.

Recommendations in the event of an accident when handling botulinum toxin

In the event of an accident when the product is being handled, whether in the powder state or reconstituted, the appropriate measures described below must be initiated immediately.

- Any spillage must be wiped up: either with an absorbent material soaked in a solution of sodium hypochlorite in the case of the powder 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 and then dried.
- If a vial is broken, proceed as stated above, carefully collect up the pieces of glass, avoiding cutting the skin and wipe up the product.
- If splashed onto the skin, wash with a solution of sodium hypochlorite and then rinse thoroughly with plenty of water.
- If splashed into the eyes, flush thoroughly with plenty of water or with an eye wash solution.
- If injured oneself (cuts, pricks oneself), proceed as above and take the appropriate medical steps according to the dose injected.