Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alluzience, 200 Speywood units/mL, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clostridium botulinum toxin type A haemagglutinin complex 200 Speywood units/ml
Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Speywood units are different from other botulinum toxin preparations.
Each vial contains 125 Speywood units in 0.625 ml of solution.
For the full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alluzience is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at maximum frown in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient.

4.2 Posology and method of administration

Posology:
Botulinum toxin product units differ depending on the medicinal products. Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Speywood units are different from other botulinum toxin preparations.

Paediatric Population
The safety and efficacy of Alluzience in children aged up to 18 years have not been established. The use of Alluzience is not recommended in patients under 18 years.

Method of administration:
Alluzience should only be administered by a physician with appropriate qualifications and expertise in this treatment and having the required equipment.

A vial of Alluzience should only be used to treat a single patient, during a single session. Remove any make-up and disinfect the skin with a local antiseptic before administration.

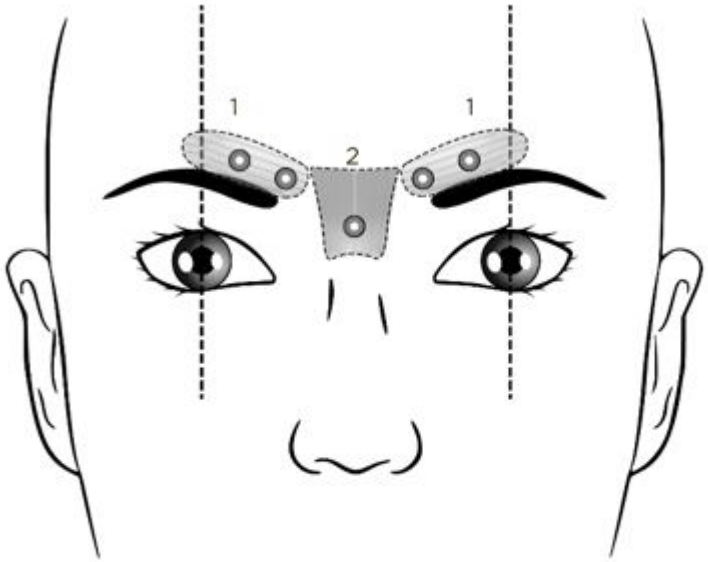
The intramuscular injections should be performed using a sterile needle with a suitable gauge.

Dosing and treatment intervals depend on assessment of the individual patient's response.

The median time to onset as reported subjectively by patients was 3 days (the majority of patients reported an effect within 2 to 3 days with some patients reporting an effect within 24 hours). An effect has been demonstrated for up to 6 months after injection.

The treatment interval should be no more frequent than every 3 months.

The recommended injection points for glabellar lines are shown below:



1. Corrugator muscles
2. Procerus muscle

Administration instructions:
The recommended dose is 0.25 ml of solution (50 Speywood units) divided into 5 injection sites, 0.05 ml of solution (10 Speywood units) administered intramuscularly into each of the 5 sites: 2 injections into each *corrugator* muscle and one into the *procerus* muscle, near the nasofrontal angle. The anatomical landmarks can be more readily identified if palpated and observed at patient maximum frown. Before injection, place the thumb or index finger firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle bevel should be pointed upward and medially during the injection. In order to reduce the risk of ptosis, avoid injections near the *levator palpebrae superioris* muscle, particularly in patients with larger brow-depressor complexes (*depressor supercilii*). Injections should be made into the central part of the *corrugator* muscle, at least 1 cm above the orbital rim.

General information
In the event of treatment failure or diminished effect following repeat injections, alternative treatment methods should be employed. In case of treatment failure after the first treatment session, the following approaches may be considered:
- Analysis of the causes of failure, e.g. incorrect muscles injected, inappropriate injection technique, and formation of toxin-neutralising antibodies
- Re-evaluation of the relevance of treatment with botulinum toxin A.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
Presence of infection at the proposed injection sites.
Presence of myasthenia gravis, Eaton Lambert Syndrome or amyotrophic lateral sclerosis.

4.4 Special warnings and precautions for use

Care should be taken to ensure that Alluzience is not injected into a blood vessel.

Injection of Alluzienceis not recommended in patients with a history of dysphagia and aspiration.
Adverse reactions possibly related to the spread of toxin effect distant from the site of administration have been reported very rarely with botulinum toxin. Swallowing and breathing difficulties are serious and can result in death.

Very rare cases of death, occasionally in the context of dysphagia, pneumopathy (including but not limited to dyspnoea, respiratory failure, respiratory arrest) and/or in patients with significant asthenia have been reported following treatment with botulinum toxin A or B.

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

Alluzienceshould be used with caution in patients with a risk of, or clinical evidence of, marked defective neuro-muscular transmission. These patients may have an increased sensitivity to agents such as botulinum toxin, and excessive muscle weakness may follow treatment.

It is essential to study the patient's facial anatomy prior to administering Alluzience. Facial asymmetry, ptosis, excessive dermatochalasis, scarring and any alterations to this anatomy, as a result of previous surgical interventions, should be taken into consideration.

Dry eyes have been reported with use of Alluzience in periocular regions (see section 4.8). Attention to this side effect is important since dry eyes may predispose to corneal disorders. Protective drops, ointment, closure of the eye by patching or other means may be required to prevent corneal disorders.

The recommended dose and frequency of administration for Alluzience must not be exceeded.

Patients treated with the recommended dose may experience exaggerated muscle weakness.

Caution should be taken when Alluzience is used in the presence of inflammation at the proposed injection sites or when the targeted muscle(s) show excessive weakness or atrophy. Cases of muscle atrophy have been reported after the use of botulinum toxin (see section 4.8).

As with all intramuscular injections, use of Alluzience is not recommended in patients who have a prolonged bleeding time.

Each vial of Alluzience must be used for a single patient treatment during a single session.

Any excess of unused product must be disposed of as detailed in Section 6.6. Specific precautions must be taken for the inactivation and disposal of any unused solution (see Section 6.6).

Antibody formation
Injections at more frequent intervals or at higher doses may increase the risk of neutralising antibody formation to botulinum toxin. Clinically, the formation of neutralising antibodies may reduce the effectiveness of subsequent treatment.

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.

Sodium content:
This medicine contains less than 1 mmol sodium (23 mg) per 125U vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with Alluzience and aminoglycosides or other agents interfering with neuromuscular transmission (e.g. curare-like agents) should only be used with caution since the effect of botulinum toxin may be potentiated.

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are only limited data from the use of botulinum toxin type A in pregnant women. Animals studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3). As a precautionary measure Alluzience should not be used during pregnancy.

Breastfeeding
It is unknown if Alluzience is excreted in human milk. Alluzience should not be used during breast-feeding.

Fertility
There are no clinical data examining the effect of Alluzience on fertility. There is no evidence of direct effect of Alluzience on fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Alluzience has a minor or moderate influence on the ability to drive and use machines. There is a potential risk of localised muscle weakness or visual disturbances linked with the use of this medicinal product which may temporarily impair the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile
A majority of adverse reactions reported with Alluzience in clinical trials were of mild to moderate intensity and reversible. The most frequently reported adverse reactions were headache and injection site reactions. The incidence of adverse reactions tended to decrease with repeated treatments.

Adverse effects related to the spread of toxin effect distant from the site of administration have been very rarely reported with botulinum toxin (excessive muscle weakness, dysphagia, aspiration pneumonia with fatal outcomes in some cases) (see section 4.4).

The adverse reactions are presented from pivotal placebo-controlled clinical trials with Alluzience and also the pivotal placebo-controlled studies with the powder formulation of the same active substance, and organised according to primary system organ class (SOC) for each preferred term in MedDRA (Table 1).

Tabulated summary of adverse reactions
The frequency of undesirable effects is classified as follows:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions Observed in Clinical Studies

Nervous system disorders	Very Common Headache Common Facial paresis* Uncommon Dizziness*
Eye disorders	Common Eyelid ptosis, eyelid oedema, brow ptosis, dry eye, lacrimation increased, asthenopia*, muscle twitching (twitching of muscles around the eye)* Uncommon Eyelid twitching, visual impairment*, vision blurred*, diplopia* Rare Eye movement disorder*
General disorders and administration site conditions	Very common Injection site reactions (periorbital haematoma, haematoma, bruising, pain, paraesthesia erythema, swelling, pruritus, oedema*, rash*, irritation*, discomfort*, stinging*), asthenia*, fatigue*, influenza-like illness*
Immune system disorders	Uncommon Hypersensitivity (eye allergy, hypersensitivity, rash)
Skin and subcutaneous tissue	Uncommon Rash*, Pruritus* Rare Urticaria*

*additional adverse drug reactions only observed with powder formulation of the same active substance in clinical trials

Post-marketing experience

System Organ Class	**Adverse Drug Reaction**	**Frequency**
Nervous system disorders	Hypoaesthesia	Not known
Musculoskeletal and connective tissue disorders	Muscle atrophy	Not known

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 HPRA Pharmacovigilance
Website: www.hpra.ie.

4.9 Overdose

Excessive doses of botulinum toxin may produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary.

Symptoms of overdose may not be present immediately following injection.

Admission to hospital should be considered in patients with symptoms of botulinum toxin overdose (e.g. a combination of muscle weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles).

4.9 Overdose

Excessive doses of botulinum toxin may produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary.

Symptoms of overdose may not be present immediately following injection.

Admission to hospital should be considered in patients with symptoms of botulinum toxin overdose (e.g. a combination of muscle weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other muscle relaxants, peripherally acting agents
ATC code: M03AX01

Mechanismof action
The primary pharmacodynamic effect of botulinum toxin type A is chemical denervation of the treated muscle, resulting in a measurable decrease of the compound muscle action potential. This causes a localized reduction of muscle activity.

Botulinum toxin type A is a muscle relaxant that temporarily weakens muscle activity. After injection, botulinum toxin type A works by blocking the transport of the neurotransmitter acetylcholine across the neuromuscular junction, located between the nerve end and the muscle fibre. The mode of action involves four main stages, all of which must function correctly for activity to occur. The action results in stopping contraction of the targeted muscles. The effect lasts for sustained periods until the junction has recovered and muscle activity returns.

Clinical efficacyand safety
A pooled total of 372 patients with moderate to severe glabellar lines were treated in 2 pivotal trials, 250 at the recommended dose of 50 Speywood units, and 122 with placebo.

The majority of patients subjectively reported an effect within 2 to 3 days, including 23% of patients within 1 day.
The proportion of responders by investigator assessment was statistically significantly higher for patients treated with Alluzience 1 month after injection compared to placebo (the primary endpoint) as well as at all other timepoints from 8 days up to 6 months (Table 2).

Table 2: Investigator Live Assessment at Maximum Frown – Responder Rate (%) at different time points

Visit after injection	**Alluzience**	**Placebo**

	(N=250)	**(N=122)**
8 days	80.0%	2.5 %
1 month	87.6%	2.5%
2 months	76.8%	1.7%
3 months	57.6 %	1.7%
4 months	36.3 %	1.8%
5 months	17.5 %	0.9%
6 months	10.0 %	0.9%

Note: A responder is defined as having a severity grade of moderate or severe at baseline and a severity grade of none or mild at a given visit.
Responder rate, the primary efficacy endpoint at Day 29, was statistically significantly different to placebo ($p<0.0001$).
Responder rates at other time points were nominally different to placebo (p-values ranging from ≤ 0.0001 to 0.0008).

The proportion of responders according to the patient self-assessment was higher for patients treated with Alluzience compared to placebo at all timepoints from 8 days up to 6 months (Table 3).

Table 3: Patient Self-Assessment – Responder Rate (%) at different time points

Visit after injection	**Alluzience (N=250)**	**Placebo (N=122)**
8 days	66.0%	4.9%
1 month	76.8%	5.7%
2 months	72.4%	2.5%
3 months	48.8%	3.4%
4 months	32.7%	4.3%
5 months	23.1%	4.3%
6 months	15.1%	2.6%

Note: A responder is defined as having a severity grade of moderate or severe at baseline and a severity grade of none or mild at a given visit
Responder rates were nominally different to placebo with $p \leq 0.0001$ at all time points

Patients' level of satisfaction 1 month following injection showed that 85.2% of the patients receiving Alluzience were either satisfied or very satisfied compared to 9% for placebo patients.

Aesthetic and psychological improvement was observed using Face-Q scales. For the facial appearance overall scale (which incorporates subject ratings for facial balance, end-of-day appearance, facial freshness, rested look, appearance when waking up and appearance under bright lights) and the psychological wellbeing scale (which incorporates subject ratings on feeling okay, self-acceptance, comfort with self, feeling good, self-liking, feeling happy, feeling attractive, and feeling confident), one month after injection, subjects treated with Alluzience showed improvement in the score for each of these scales compared to subjects who were treated with placebo (nominal $p<0.0001$).

A total of 595 patients received up to 5 treatment cycles of Alluzience in a 12 months long-term open-label phase III study. Efficacy was maintained over the 12 months period, by the investigator assessment, the patient assessment, patient satisfaction and FACE-Q questionnaires.

The proportion of responders at maximum frown, determined by the investigator 1 month after the injection, was maintained over repeated injection cycles (between 82.2% and 87.8%). The corresponding proportions 3 months after injection ranged between 45.3% and 56.8% across the 5 treatment cycles.

Patients (595 in total) receiving Alluzience over a 12 months period were tested for antibody formation. No patients tested positive for toxin-neutralising antibodies.

5.2 Pharmacokinetic properties

Alluzience is not expected to be present in the peripheral blood at measurable levels following intramuscular injection at the recommended dose. Pharmacokinetic studies have therefore not been performed.

5.3 Preclinical safety data

In reproductive studies in rats and rabbits, severe maternal toxicity associated with implantation losses was observed at high doses. At doses corresponding to 60 to 100 times the human recommended dose (50 Speywood units) in rabbits and rats respectively, no embryofetal toxicity was observed. No teratogenic effects were observed in these species. In rats, fertility of the males and females was decreased due to reduced mating secondary to muscle paralysis at high doses.

In a chronic toxicity study performed in rats, there was no indication of systemic toxicity at doses corresponding to 75 times the human recommended dose (50 Speywood units) divided equally between right and left gluteus muscles.

Studies on acute toxicity, chronic toxicity and local tolerance at the injection site showed no unusual adverse local or systemic effects at clinically relevant dose levels.

Environmental Risk Assessment (ERA)
Alluzience is unlikely to represent a risk for the environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
Sucrose
Sodium chloride
Polysorbate 80
Hydrochloric acid for pH adjustment
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

12 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep vials in the outer carton in order to protect from light.

After taking the vial from the refrigerator, it is recommended to allow the vial to reach room temperature.

Alluzience may be held at temperatures up to a maximum of 25°C for a single period of 12 hours when unopened and protected from light. Alluzience should be discarded if not used within 12 hours of removal from refrigeration.

Once the vial is opened, the product should be used immediately.

6.5 Nature and contents of container

Nature of container/closure
Type 1 glass vial, butyl rubber closure and aluminum overseal with a polypropylene flip-off top.

Contents of container
Each vial contains 125 Speywood units of *Clostridium botulinum* type A toxin-haemagglutinin complex in 0.625 ml of solution. Clear colourless solution.

Pack sizes:

Individual pack size:
Pack containing 1 or 2 vials of Alluzience 200 Speywood units/ml solution for injection.
Multiple Pack:
A multipack contains 6 individual packs, each including 2 vials of Alluzience 200 Speywood units/ml solution for injection

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Immediately after treatment of the patient, any residual Alluzience which may be present in either vial or syringe should be inactivated with dilute hypochlorite solution (1% available chlorine).
Spillage of Alluzience should be wiped up with an absorbent cloth soaked in dilute hypochlorite solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

RECOMMENDATIONS SHOULD ANY INCIDENT OCCUR DURING THE HANDLING OF BOTULINUM TOXIN

- Any spills of the product must be wiped up with dry, absorbent material.
- The contaminated surfaces should be cleaned using absorbent material impregnated with a solution of sodium hypochlorite (bleach), then dried.
- If a vial is broken, proceed as mentioned above by carefully collecting the pieces of broken glass and wiping up the product, avoiding any cuts to the skin.
- If the product comes into contact with the skin, wash the affected area with a solution of sodium hypochlorite (bleach) then rinse abundantly with water.
- If product enters into contact with the eyes, rinse thoroughly with plenty of water or with an ophthalmic eyewash solution.
- If product enters into contact with a wound, cut or broken skin, rinse thoroughly with plenty of water and take the appropriate medical steps according to the dose injected.

These instructions for use handling and disposal should be strictly followed.

7 MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

8 MARKETING AUTHORISATION NUMBER

PA1613/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th September 2021

10 DATE OF REVISION OF THE TEXT

April 2023