# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Azzalure, 125 Speywood units, powder for solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Botulinum toxin type A* Quantity corresponding to 125 Speywood units (U)** for one vial.

**Clostridium botulinum* toxin A haemagglutinin complex
** The Speywood units of Azzalure are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.

For the full list of excipients see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for solution for injection.
The powder is white.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Azzalure is indicated for the temporary improvement in the appearance of moderate to severe:
- Glabellar lines (vertical lines between the eyebrows) seen at maximum frown and/or
- Lateral canthal lines (crow's feet lines) seen at maximum smile 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 units are different depending on the medicinal products. The Speywood units of Azzalure are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.

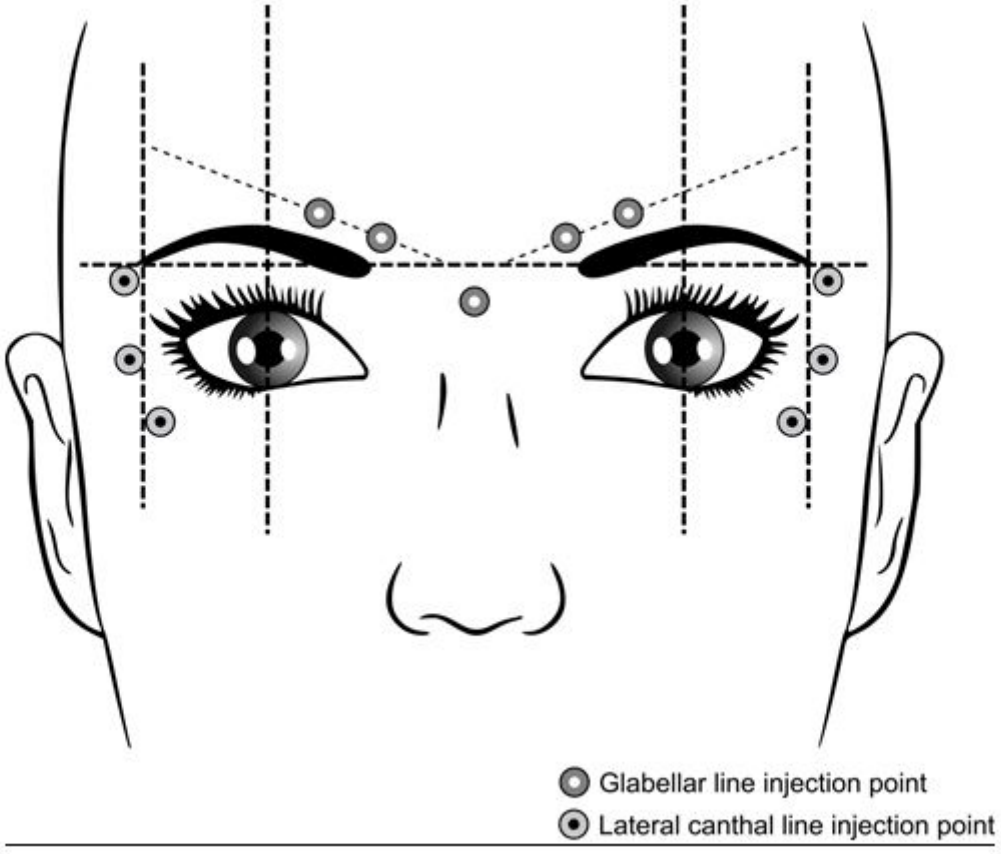
Paediatric population
The safety and efficacy of Azzalure in individuals aged up to 18 years have not been established. The use of Azzalure is not recommended in subjects under 18 years.

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

Once reconstituted, Azzalure should only be used to treat a single patient, during a single session.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.
Remove any make-up and disinfect the skin with a local antiseptic.
Intramuscular injections should be performed using a sterile 29 - 30 gauge needle.

The treatment interval depends on the individual patient's response after assessment. Treatment interval with Azzalure should not be more frequent than every three months.

The recommended injection points for glabellar lines and lateral canthal lines are described below:




***Glabellar lines***
The recommended dose is 50 Speywood units (0.25 ml of reconstituted solution) of Azzalure to be divided into 5 injection sites, 10 Speywood units (0.05 ml of reconstituted solution) are to be administered intramuscularly, at right angles to the skin, into each of the 5 sites: 2 injections into each *corrugator* muscle and one into the *procerus* muscle near the nasofrontal angle as shown above.

The anatomical landmarks can be more readily identified if observed and palpated at maximal 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 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 in the *corrugator* muscle must be made into the central part of that muscle, at least 1 cm above the orbital rim.

In clinical studies, an optimal effect in glabellar lines was demonstrated for up to 4 months after injection. Some patients were still responders at 5 months (see section 5.1).

***Lateral Canthal lines***
The recommended dose per side is 30 Speywood units (60 Speywood units for both sides, 0.30 ml of reconstituted solution) of Azzalure, to be divided into 3 injection sites; 10 Speywood units (0.05 ml of reconstituted solution) are to be administered intramuscularly into each injection point. Injection should be lateral (20 - 30° angle) to the skin and very superficial. All injection points should be at the external part of the *orbicularis oculi* muscle and sufficiently far from the orbital rim (approximately 1 - 2 cm) as shown above.

The anatomical landmarks can be more readily identified if observed and palpated at maximal smile. Care must be taken to avoid injecting the *zygomaticus major/minor* muscles to avoid lateral mouth drop and asymmetrical smile.

<u>General information</u>
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.

The efficacy and safety of repeat injections of Azzalure has been evaluated in Glabellar lines up to 24 months and up to 8 repeat treatment cycles and for Lateral Canthal lines up to 12 months and up to 5 repeat treatment cycles.

**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 Azzalure is not injected into a blood vessel.

Pre-existing Neuromuscular Disorders
Azzalure should be used with caution in patients with a risk of, or clinical evidence of, marked defective neuro-muscular transmission. Such patients may have an increased sensitivity to agents such as Azzalure, which may result in excessive muscle weakness.

Injection of Azzalure is not recommended in patients with a history of dysphagia and aspiration.

Local and distant spread of toxin effect
Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin. Patients treated with therapeutic doses may experience exaggerated muscle weakness. Swallowing and breathing difficulties are serious and can result in death.

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

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

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

Caution should be taken when Azzalure is used in the presence of inflammation at the proposed injection site(s) or when the targeted muscle shows excessive weakness or atrophy.

As with all intramuscular injections, Azzalure treatment is not recommended in patients who have a prolonged bleeding time.

Dry eye has been reported with the use of Azzalure in the treatment of glabellar lines and lateral canthal lines (see section 4.8). Reduced tear production, reduced blinking, and corneal disorders, may occur with the use of botulinum toxins, including Azzalure.

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

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

It is mandatory that Azzalure is used for one single patient treatment only during a single session. 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 6.6).

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**

Concomitant treatment of Azzalure 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 type A may be potentiated.

No interaction studies have been performed. No other interactions of clinical significance have been reported.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**
Azzalure should not be used during pregnancy. There are no adequate data from the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown.

**Breast-feeding**
There is no information on whether Azzalure is excreted in human milk. The use of Azzalure during lactation cannot be recommended.

**Fertility**
There are no clinical data from the use of Azzalure on fertility. There is no evidence of direct effect of Azzalure on fertility in animal studies (see section 5.3).

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

Approximately 3800 patients were exposed to Azzalure in the different clinical trials.

Based on placebo-controlled clinical trials, the observed rates of adverse reactions after the first injection of Azzalure were 22.3% for the treatment of glabellar lines (16.6 % for placebo) and 6.2 % for the treatment of lateral canthal lines (2.9 % for placebo). Most of these events were of mild to moderate severity and reversible.

The most frequent undesirable reactions were headache and injection site reactions for glabellar lines and headache, injection site reactions and eyelid oedema for lateral canthal lines. In general, treatment/injection technique related reactions occurred within the first week following injection and were transient. The incidence of treatment/injection technique related reactions decreased over repeat cycles. Undesirable effects may be related to the active substance, the injection procedure, or a combination of both.

The safety profile of Azzalure for concomitant treatment of glabellar lines and lateral canthal lines was evaluated in the open label part of the phase III study; the nature and frequency of adverse reactions were comparable to what was observed when patients were treated for the individual indications.

The frequency of undesirable reactions 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).

***For glabellar lines:***

| System Organ Class | Adverse Reactions |
|---|---|
| Nervous system disorders | Very Common<br>Headache<br>Common<br>Temporary facial paresis (due to temporary paresis of facial muscles proximal to injection sites, predominantly describes brow paresis)<br>Uncommon |

| | |
|---|---|
| | Dizziness |
| Eye disorders | Common<br>Asthenopia, Eyelid ptosis, Eyelid oedema, Lacrimation increased, Dry eye, Muscle twitching (twitching of muscles around the eyes)<br>Uncommon<br>Visual impairment, Vision blurred, Diplopia<br>Rare<br>Eye movement disorder |
| Skin and subcutaneous tissue disorders | Uncommon<br>Pruritus, Rash<br>Rare<br>Urticaria |
| General disorders and administration site conditions | Very Common<br>Injection site reactions (e.g. erythema, oedema, irritation, rash, pruritus, paraesthesia, pain, discomfort, stinging and haematoma) |
| Immune system disorders | Uncommon<br>Hypersensitivity |

***For lateral canthal lines:***

| **System Organ Class** | **Adverse Reactions** |
|---|---|
| Nervous system disorders | Common<br>Headache<br>Temporary facial paresis (temporary paresis of facial muscles proximal to injection sites) |
| Eye disorders | Common<br>Eyelid oedema<br>Eyelid ptosis<br>Uncommon<br>Dry eye |
| General disorders and administration site conditions | Common<br>Injection site reactions (e.g. haematoma, pruritus and oedema) |

Adverse reactions resulting from distribution of the effects of the toxin to sites remote from the site of injection have been very rarely reported with botulinum toxin (excessive muscle weakness, dysphagia, aspiration pneumonia with fatal outcomes in some cases) (see section 4.4).

Post-marketing experience

| **System Organ Class** | **Adverse Drug Reaction** | **Frequency** |
|---|---|---|
| General disorders and administration site conditions | Asthenia, fatigue,influenza-like illness | Not known |
| Immune system disorders | Hypersensitivity | Not known |
| Nervous system disorders | Hypoaesthesia | Not known |
| Musculoskeletal and connective tissue disorders | Muscle atrophy | Not known |

Reporting of suspected adverse reactions

Reporting of 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**

Excessive doses of botulinum toxin may be expected to 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 should be instigated if necessary.

Symptoms of overdose may not present immediately following injection.

Admission to hospital should be considered in patients presenting symptoms of botulinum toxin A poisoning (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

The primary pharmacodynamic effect of *Clostridium botulinum* toxin type A is due to chemical denervation of the treated muscle resulting in a measurable decrease of the compound muscle action potential, causing a localised reduction of, or paralysis in, muscle activity.
Botulinum toxin type A is a muscle relaxant that temporarily weakens the muscles' 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 of botulinum toxin type A involves four main stages, all of which must function correctly for activity to occur. The action results in stopping the muscular contraction of the targeted muscles. The effect lasts for sustained periods until the junction has recovered and muscle activity returns.

**Clinical data**
During the clinical development of Azzalure, more than 4500 patients were included in the different clinical trials and approximately 3800 patients were exposed to Azzalure.

***Glabellar lines***
In clinical studies, 2032 patients with moderate to severe glabellar lines have been treated at the recommended dose of 50 Speywood units. Of these, 305 were treated with 50U in two pivotal Phase III double-blind placebo-controlled studies and 1200 treated with 50U in a long-term open-label repeated dose Phase III study. The remaining patients were treated in supportive and dose-ranging studies.

The median time to onset of response was 2 to 3 days following treatment, with the maximum effect observed at day thirty. In both pivotal placebo-controlled phase III studies, Azzalure injections significantly reduced the severity of glabellar lines for up to 4 months. The effect was still significant after 5 months in one of the two pivotal studies.

Thirty days following injection, the assessment of the investigators showed that 90% (273/305) of patients had responded to treatment (exhibited no or mild glabellar lines at maximum frown), compared to 3% (4/153) placebo-treated patients. Five months after injection, 17% (32/190) of patients treated with Azzalure were still responding to treatment compared to 1% (1/92) of placebo treated patients in the concerned study. The patients' own assessment at maximum frown after thirty days gave a response rate of 82% (251/305) for those treated with Azzalure and 6% (9/153) for those treated with placebo. The proportion of patients exhibiting a two-grade improvement according to the investigator assessment at maximum frown, was 77% (79/103) in the one pivotal Phase III study where this was assessed.

A subset of 177 patients had moderate or severe glabellar lines at rest prior to treatment. Assessment by investigators of this population, thirty days after treatment, showed that 71% (125/177) of Azzalure-treated patients were considered responders versus 10% (8/78) of placebo-treated patients.

The long-term repeat dose open label study showed that the median time to onset of response of 3 days was maintained across repeated dose cycles. The responder rate at maximum frown as determined by the investigator at day 30 was maintained over repeated cycles (ranging between 80% and 91% over the 5 cycles). The responder rate at rest over repeated dose cycles was also consistent with the single dose studies, with 56% to 74% of Azzalure-treated patients considered by investigators to be responders thirty days after treatment.

***Lateral Canthal lines***
In clinical studies, 308 patients with moderate to severe lateral canthal lines at maximum smile have been treated at the recommended dose of 30 Speywood units per side in double blind studies. Of these, 252 were treated in a Phase III double-blind placebo controlled study and 56 patients were treated in a double-blind Phase II dose-ranging study.

In the phase III study, Azzalure injections significantly reduced the severity of lateral canthal lines compared with placebo ($p \leq 0.001$) at 4, 8 and 12 weeks (assessed at maximum smile by the investigators). For the subjects' assessment of satisfaction with the appearance of their lateral canthal lines, there was a statistically significant difference between Azzalure and placebo ($p \leq 0.010$) in favour of Azzalure at 4, 8, 12 and 16 weeks.

The primary efficacy endpoint was at 4 weeks following injection: the assessment of the investigators showed that 47.2% (119/252) of patients had responded to treatment (no or mild lateral canthal lines at maximum smile), compared to 7.2% (6/83) placebo-treated patients.

In a post-hoc analysis, at the same point, 4 weeks following injection, 75% (189/252) of Azzalure treated patients had at least 1 grade improvement at maximum smile compared with only 19% (16/83) of placebo-treated subjects.

A total of 315 subjects entered the open label extension phase of the Phase III study in which they could be treated concomitantly for both lateral canthal lines and glabellar lines.
Patients treated with Azzalure in the double-blind and open label phases of the Phase III received a median of 3 treatments for lateral canthal lines. The median interval between injections for lateral canthal lines, which was largely determined by the protocol design, ranged from 85 to 108 days. The results showed that efficacy is maintained with repeated treatments over the period of one year.
The patient satisfaction levels at weeks 4, 16 and 52 show after the first treatment with Azzalure that 165/252 subjects (65.5%) were either very satisfied or satisfied with the appearance of their LCLs.
At week 16, 4 weeks after either a second Azzalure treatment for those randomised to Azzalure in Part A or the first treatment for those randomised to placebo the proportion who were very satisfied or satisfied was 233/262 (89.0%). At week 52 when subjects could have had up to five cycles of Azzalure treatment with the last one being at week 48 the proportion of very satisfied/satisfied subjects was 255/288 (84.7%).

No patient tested positive for toxin-neutralising antibodies after receiving repeated treatments with Azzalure over one year.

**5.2 Pharmacokinetic properties**

Azzalure is not expected to be present in the peripheral blood at measurable levels following IM injection at the recommended dose. Therefore pharmacokinetic studies have not been performed with Azzalure.

**5.3 Preclinical safety data**

In reproductive studies in rats and rabbits, severe maternal toxicity associated with implantation loses was observed at high doses. At doses corresponding to 60 to 100 times the human recommended dose (50U) 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 (50U) divided equally between the right and left gluteus muscles.
Studies on acute toxicity, chronic toxicity and local tolerance at the injection site did not show unusual adverse local or systemic effects at clinically relevant dose levels.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Human albumin 200 g/L
Lactose monohydrate.

**6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

**6.3 Shelf life**

2 years.

**Reconstituted solution:**
Chemical and physical in-use stability has been demonstrated for 24 hours between 2-8°C. From a microbiological point of view, unless the method of reconstituting precludes the risks of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

**6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For storage of the reconstituted medicinal product see section 6.3.

**6.5 Nature and contents of container**

125 Speywood units in a powder in a vial (Type I glass), with a stopper (halobutyl) and seal (aluminium).
Pack size of 1 or 2 vial(s).
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

The instructions for use, handling and disposal should be strictly followed.
Reconstitution should be performed in accordance with good practice rules, particularly in the respect of asepsis.
Azzalure has to be reconstituted with a sodium chloride 9 mg/ml (0.9%) solution for injection. As per the dilution table below, the requested amount of sodium chloride 9 mg/ml (0.9%) solution for injection has to be drawn up into a syringe in order to obtain a reconstituted clear and colourless solution at the following concentration:

| Amount of solvent added (0.9 % sodium chloride solution) to a 125 U vial | Resulting dose |
|---|---|
| 0.63 ml | 10 U per 0.05 ml |
| 1.25 ml | 10 U per 0.1 ml |

The accurate measurement of 0.63 ml or 1.25 ml can be achieved using syringes graduated in 0.1 ml and 0.01 ml increments.

RECOMMENDATIONS FOR THE DISPOSAL OF CONTAMINATED MATERIALS

Immediately after use and prior to disposal, unused reconstituted Azzalure (in the vial or in the syringe) should be inactivated with 2ml of dilute sodium hypochlorite solution at 0.55 or 1% (Dakin's solution).
Used vials, syringes and materials should not be emptied and must be discarded into appropriate containers and 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: either using absorbent material impregnated with a solution of sodium hypochlorite (bleach) in case of the powder, or with dry, absorbent material in case of reconstituted product.
- 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**

PA1613/001/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 26th March 2010
Date of last renewal: 28th January 2014

**10 DATE OF REVISION OF THE TEXT**

July 2022