AZZALURE
Botulinum Toxin Type A

Dosage and Administration

Information for Prescribing and Practicing Specialists

According to the European Risk Management Plan For Botulinum Toxin Products

GALDERMA

Introduction

This brochure contains important information regarding the use of Azzalure® (botulinum toxin type A) and includes recommendations stated in the Summary of Product Characteristics for Azzalure®.

Its purpose is to promote:

- Understanding of the mode of action of Azzalure®
- Understanding of potential adverse events associated with remote distribution of effect of botulinum toxin and risk factors for serious adverse events
- Awareness that botulinum toxin units are not interchangeable from one product to another
- Appropriate injection technique
- Appropriate reconstitution, dose and treatment intervals
- Education of patients and their caregivers on the following subjects:
    - What causes wrinkles
    - Various treatments of wrinkles
    - The mode of action of botulinum toxin in the treatment of glabellar lines and the treatment procedure
    - The duration of effect and treatment intervals
    - The description of the usual side effects of Azzalure®, signs of spread of the botulinum toxin to distant sites, description of possible severe adverse reactions observed with botulinum toxin A and risk factors.
    - What the patients should do if they experience any of these symptoms

Treating physicians should have the appropriate qualifications and expertise or training in the use of botulinum toxin type A.

If more copies of this educational material are required please contact Galderma (UK) Ltd, Tel: +44 1923 208950, Fax: +44 1923 208998

Azzalure® mode of action

When injected into the target muscle, Azzalure® (botulinum toxin type A) binds to the presynaptic nerve endings, crosses the pre-synaptic nerve membrane and blocks release of the neurotransmitter acetylcholine. This results in a reversible, inhibition of neurotransmission at the neuromuscular junction of the injected muscles (1-5)

Azzalure® effect

After injection in the glabellar muscles (corrugators and procerus), moderate to severe glabellar wrinkles are reduced. The median time to onset of response is 2 to 3 days following treatment.

An optimal effect was demonstrated for up to 4 months after injection. Some patients were still responders at 5 months .

The treatment interval depends on the individual patient's response after assessment. Treatment interval should not be more frequent than every 3 months (6-10).

Potential risks associated with the use of Azzalure®

The nature of the potential adverse reactions is consistent with the pharmacological action of botulinum toxin type A and the injection procedure. It can include injection site reactions, headaches or clinically detectable effects in the muscles adjacent to the target muscles injected.

Every effort should be made to avoid injection of excess botulinum toxin (i.e. overdosing) which can bind to sites outside the target area (11-14) or very rarely lead to remote effect of botulinum toxin A.

Knowledge of facial anatomy, training on the injection of botulinum toxin A in the glabella, consideration of the patient's goal, examination of the patient's facial mimics and wrinkles and the use of Azzalure® according to the recommendations in the SmPC, i.e., for dose, product reconstitution and injection sites, will optimise treatment effect and safety.

The most frequently occurring adverse reactions are headache and injection site reactions. In general, treatment/injection technique related reactions occur within the week following the injection and are transient.

Ocular Events

Ocular events, which are usually dose- and technique-related, were found in studies in a very low number of patients. The incidence of eyelid ptosis ranged from 0% to 2.5% and tended to decrease with repeated treatments.

Eyelid oedema, dry eye and lacrimation could also result from unwanted spread of botulinum toxin away from the site of injection. Other possible ocular effects are asthenopia, secondary muscle twitching, visual disturbance, vision blurred, diplopia and rarely, eye movement disorder.

Systemic Events

Serious adverse events suspected to be related to the remote distribution of effects of botulinum toxin outside the target tissue have been reported with all botulinum toxin preparations, including dysphagia and rare cases of excessive muscle weakness, or aspiration pneumonia.

There have been very rare reports of adverse events with fatal outcome. In clinical trials conducted with Azzalure® in the treatment of moderate to severe glabellar lines, there have been no adverse events (serious or non-serious) suspected to be related to the remote distribution of effects of botulinum toxin outside the target tissue.

Patients with:

- underlying neurological disorders
- history of swallowing difficulties
- history of breathing difficulties
- history of aspiration
- concomitant drug treatment interfering directly or indirectly with the neuromuscular function (e.g. aminoglycosides, curare-like non-depolarising blockers) are at increased risk of these side effects and should be treated with extreme caution and only if the benefit of the treatment with botulinum toxin is considered to outweigh the risk.

In order to minimize any risk of serious spread reactions of botulinum toxin, it is essential that the posology, warnings and precautions are strictly followed as stipulated in the SmPC.

Patients should be informed about the potential risks associated with the use of botulinum toxin type A, instructed to recognise early signs of important undesirable effects (difficulties swallowing, speaking, breathing or excessive muscle weakness, allergic reaction) and urged to seek urgent medical advice if these symptoms are experienced. They also should be instructed to inform other health professionals about their use of botulinum toxin type A when seeking treatment for other conditions.

The development of neutralizing antibodies to botulinum toxin type A that could reduce or abolish response to repeat administrations is extremely rare in indications requiring low therapeutic doses. However, to reduce the risk of secondary non-response the treatment interval should not be less than 3 months.

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, injection technique, and formation of toxin-neutralising antibodies;
- Re-evaluation of the relevance of treatment with botulinum toxin A

Adverse event reporting

Please remember that any adverse event following the use of botulinum toxin products should be reported to the marketing authorisation holder and/or local regulatory authorities, in the usual way.

For further information, please contact:
Galderma (UK) Ltd.
Phone: +44 1923 208950
Fax: +44 1923 208998

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website:www.hpra.ie; E-mail:medsafety@hpra.ie.

Botulinum toxin units are not interchangeable

The potency of Azzalure® is measured in Speywood units and correlates with the efficacy in clinical use. The units of Azzalure® are specific to its preparation and are not interchangeable with units of other preparations of botulinum toxins.

Approved indications for Azzalure® in Ireland

Adults

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

Children

There is no relevant indication for the use of Azzalure® in patients under the age of 18. The safety and effectiveness of Azzalure® in individuals under 18 years of age have not been demonstrated.

Reconstitution, storage and disposal

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 solution at a concentration of 10 U/0.05 ml;

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

The accurate measurement of 0.63ml can be achieved using 1ml syringes, graduated in 0.1 ml and 0.01 ml increments.

The stopper of the Azzalure® vial should be cleaned with alcohol and then the solvent introduced slowly into the vial. The vial should be mixed gently to dissolve the vial's contents. This provides a clear solution containing 125 Speywood Units of active substance at a concentration of 10 Speywood U per 0.05ml of 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. Azzalure® should not be frozen.

Once reconstituted, Azzalure® should only be used to treat a single patient, during a single session.

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% (bleach).

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.

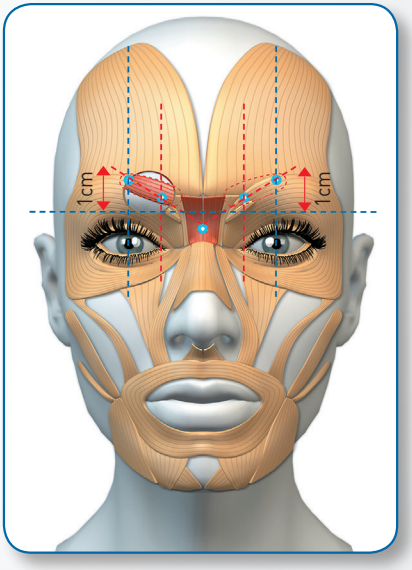
Dosage and administration of Azzalure®

- 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.
- Azzalure® should only be administered by physicians with appropriate qualifications and expertise in this treatment and having the required equipment.
- The dosage regimen recommended in the SmPC should be followed. Treatment should be repeated as required to prevent recurrence of the symptoms, but no more frequently than recommended in the SmPC.

Treatment of moderate to severe glabellar lines with Azzalure®

Administration instructions:

- Remove the make-up and disinfect the skin with a local antiseptic.
- Intramuscular injections should be performed at right angles to the skin using a sterile 29-30 gauge needle.
- The recommended dose is 50 Speywood units (0.25 ml of the reconstituted solution) of Azzalure® to be divided into 5 injection sites, 10 Speywood units (0.05 ml of the reconstituted solution) are to be administered intramuscularly into each of the 5 sites: 2 injections into each corrugator muscle and one into the procerus muscle near the nasofrontal angle as shown below:



- 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.
- The physician must ensure that he avoids intravascular injection.

Planning of a detailed discussion with the patients and their caregivers on the benefit/risk ratio, potential risks and availability of the educational material for patients

Before starting treatment with Azzalure® the patient must be informed about

- The causes of glabellar lines
- The alternative and complementary treatment options available
- The treatment objectives and expected outcome
- Possible side effects and known risk factors, i.e. the benefit/risk ratio.
- Who to inform and what to do when the patient experiences a side effect to botulinum toxin

Further information regarding the use and safety of Azzalure®

For further information, please contact:

Galderma (UK) Ltd.

Phone: +44 1923 208950

Fax: +44 1923 208998

References

1. Tang-Liu, Diane D. I-botulinum neurotoxin-complex versus I-botulinum-free neurotoxin: time course of tissue distribution. Toxicon 2003;42:461-469.
2. Tang-Liu DD, Aoki KR, Dolly JO, et al. Intramuscular injection of 125I-botulinum neurotoxin-complex versus 125I botulinum-free neurotoxin: time course of tissue distribution. Toxicon 2003;42:461-469.
3. Poulain B, Popoff M, Molgo J. How do botulinum neurotoxins block neurotransmitter release: from botulism to the molecular mechanism of action. The Botulinum J 2008;1:14-87.
4. Rogozhin AA, Pang KK, Bukharavea E. Recovery of mouse neuromuscular junctions from single and repeated injections of botulinum neurotoxin A. J Physiol 2008;586;3163-3182.
5. Rossetto O, Montecucco C. Chapter 2. How botulinum toxins work. In: Moore P, Naumann M, editors. Handbook of Botulinum Toxin Treatment. 2nd Ed. Blackwell Science 2003.
6. Monheit G, Carruthers A, Brandt F, Rand R. A randomized, double-blind, placebo-controlled study of botulinum toxin type A for the treatment of glabellar lines: determination of optimal dose. Dermatol Surg 2007;33(1):S51-9.
7. Ascher B, Zakine B, Kestemont P, et al. A multicentre, randomized, double-blind, placebo-controlled study of efficacy and safety of three doses of botulinum toxin A in the treatment of glabellar lines. J Am Acad Dermatol 2004;51(2):223-33.
8. Ascher B, Zakine B, Kestemont P, et al. Botulinum Toxin A in the treatment of glabellar lines: scheduling the next injection. Aesth Surg J 2005;365-376.
9. Rzany B, Ascher B, Fratila A, et al. Efficacy and safety of 3- and 5-injection patterns (30 and 50 U) of botulinum toxin A (Dysport) for the treatment of wrinkles in the glabella and the central forehead region. Arch Dermatol 2006;142(3):320-326.
10. Rzany B, Dill-Mueller D, Grablowitz, et al. Repeated botulinum toxin A injections for the treatment lines in the upper face: a retrospective study of 103 treatments in 945 patients. Dermatol Surg 2007;33(1):S18-25.
11. Elson ML. Evaluation and treatment of the aging face. In: Evaluation and Treatment of the Aging Face, Elson M, ed. Springer-Verlag, New York, 1995, 1-9.
12. Borodic, GE, R Ferrante, LB Pearce, et al. Histologic assessment of dose-related diffusion and muscle fiber response after therapeutic botulinum A toxin injections. Mov Disord, 1994. 9(1):31-9
13. Shaari, CM and I Sanders. Quantifying how location and dose of botulinum toxin injections affect muscle paralysis. Muscle Nerve, 1993. 16(9):964-9
14. Eleopra R, Tugnoli V, Caniatti L, De Grandis D. Botulinum toxin treatment in the facial muscles of humans: evidence of an action in untreated near muscles by peripheral diffusion. Neurology 1996;46:1158-1160.

AZZ/026/0415a(1)
Date of preparation: November 2015