▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – RELFYDESS® (RELABOTULINUMTOXINA) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

RELFYDESS, 100 units/mL, solution for injection

relabotulinumtoxinA, purified Botulinum toxin type A, free from complex proteins

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BOTULINUM TOXIN UNITS ARE NOT INTERCHANGEABLE FROM ONE PRODUCT TO ANOTHER.

Each vial of RELFYDESS contains 150 units in 1.5 mL of solution for injection of relabotulinumtoxinA.

RelabotulinumtoxinA is manufactured from an established Working Cell Bank that is grown in culture media. The post-cultured product is harvested and purified using several steps to obtain a botulinum neurotoxin of serotype A1, free from complexing proteins and animal or human derived proteins.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for Injection

Clear, colourless to pale yellow solution

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RELFYDESS is indicated in adult patients for the temporary improvement in the appearance of:

- Moderate to severe glabellar lines at maximum frown
- Moderate to severe lateral canthal lines seen at maximum smile

4.2 DOSE AND METHOD OF ADMINISTRATION

RELFYDESS should only be administered by trained practitioners with appropriate qualifications and expertise in the treatment of glabellar lines and lateral canthal lines and having the required equipment.

THE POTENCY UNITS ARE SPECIFIC TO RELFYDESS AND ARE NOT INTERCHANGEABLE WITH OTHER PREPARATIONS OF BOTULINUM TOXIN.

Re-treatment of RELFYDESS should be administered no more frequently than every twelve weeks. Consideration of the cumulative dose is necessary when treating adult patients with RELFYDESS for glabellar lines and lateral canthal lines, alone or in combination, if other botulinum toxin products are or have been used to treat other indications approved for

those products.

Dosage

RELFYDESS is ready-to-use with a concentration of 10 units per 0.1 mL and no reconstitution is required.

Dosing Instructions for RELFYDESS

Treatment(s)	Total Recommended Dose	Dose per injection
Glabellar Lines (GL)	50 units/0.5 mL	5 injections of 10 units/0.1 mL: 2 injections on each side at the *corrugator* muscle and 1 injection at the *procerus* muscle near the nasofrontal angle (see **Figure 1**)
Lateral Canthal Lines (LCL)	60 units/0.6 mL	6 injections of 10 units/0.1 mL: 3 injections on each side at the orbicularis oculi muscle (see **Figure 2**)
Combined treatment of Glabellar Lines and Lateral Canthal Lines	110 units/1.1 mL	11 injections total of 10 units/0.1 mL for combined GL and LCL

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 beyond 12 months has not been evaluated.

Paediatric population

The safety and efficacy of RELFYDESS in children aged up to 18 years have not been established.

The use of RELFYDESS is not recommended in patients under 18 years.

Method of administration

Intramuscular use.

Each vial should be used for a single patient during a single treatment session only. Residual product after the treatment should be discarded.

Precaution to be taken before manipulating or administering the product
For instructions for use, precaution before manipulating or administering the product, handling and disposal of the vials (see Section 6.6 SPECIAL PRECAUTIONS FOR STORAGE).

Onset of action reported within 1 day (up to 39% and 34% in glabellar and lateral canthal lines, respectively). An effect has been demonstrated for 6 months after injection.

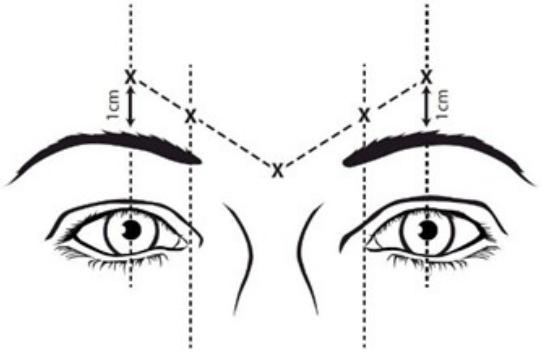
Glabellar lines

The recommended dose for the treatment of glabellar lines in adults is a total of 50 units/0.5 mL administered by intramuscular injection divided equally (10 units/0.1 mL per injection) into each of the 5 intramuscular injection sites (see **Figure 1**): 2 injections on each side at the corrugator muscle and 1 injection at the procerus muscle near the nasofrontal angle.

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

- Avoid injections near the levator *palpebrae superioris* muscle, particularly in patients with larger brow-depressor complexes.
- Lateral *corrugator* injections should be placed at least 1 cm above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
- Avoid injecting closer than 1 centimetre above the central eyebrow.

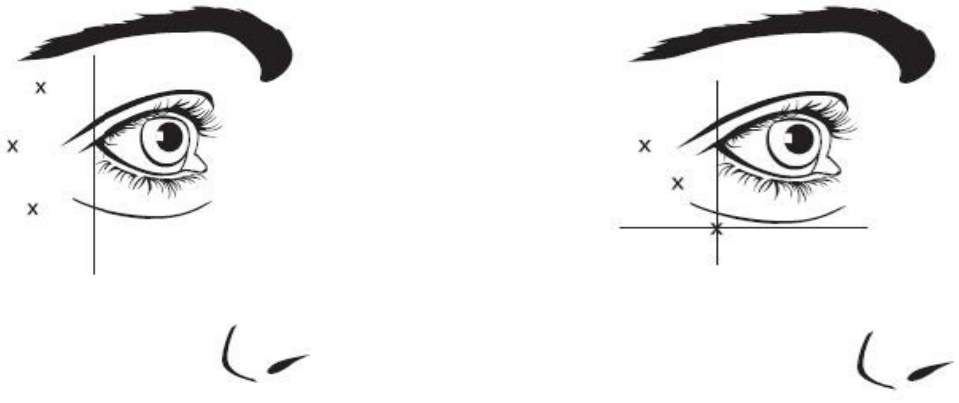
Figure 1: Injection site locations for Glabellar Lines



Lateral Canthal Lines

The recommended dose for the treatment of lateral canthal lines in adults is a total of 60 units/0.6 mL administered by intramuscular injection divided equally into 10 units/0.1 mL into each of the 6 intramuscular injection sites (see **Figure 2**: Option 1 and Option 2): 3 injections (30 units/0.3 mL) on each side at the *orbicularis oculi* muscle. When lines in the lateral canthal region appear both above and below the lateral canthus, inject per Option 1. In case lines in the lateral canthal region are mainly below the lateral canthus, inject per Option 2.

Figure 2: Injection site locations Lateral Canthal Lines



Option 1: Above and below lateral canthus **Option 2:** Below lateral canthus

Lateral Canthal line 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.

Combined treatment

For combination treatment of glabellar lines and lateral canthal lines, the respective individual

dosing and administration should be followed for a total dose of 110 units/1.1 mL of RELFYDESS.

The recommended dose for the treatment of glabellar lines is 50 units/0.5mL (10 units/0.1 mL per injection) into each of 5 intramuscular injection sites and for lateral canthal lines is 60 units/0.6 mL (10 units/0.1 mL) in each of 6 intramuscular injection sites).

4.3 CONTRAINDICATIONS

Hypersensitivity to any botulinum toxin or to any of the excipients listed in section 6.1 List of Excipients.

Presence of infection at the proposed injection sites.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Lack of interchangeability between botulinum toxin products

The potency units of RELFYDESS are specific to the preparation and assay method utilised. They are not interchangeable with the other preparations of botulinum toxin products and, therefore units of biological activity of RELFYDESS cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method (see Section 4.2 DOSE AND METHOD OF ADMINSTRATION).

Hypersensitivity reactions

Serious and/or immediate hypersensitivity reactions have been reported for botulinum toxin products. Emergency facilities including appropriate equipment and drugs (e.g., epinephrine) to treat anaphylaxis should therefore be available. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. If such a reaction occurs, further injection of RELFYDESS should be discontinued, and appropriate medical therapy immediately instituted.

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 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The symptoms are consistent with the mechanism of action of botulinum toxins and may include asthenia, generalised muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection.

Swallowing and breathing difficulties are serious and can result in death. More specifically, following treatment with botulinum toxin, very rare cases of death have been reported in the context of patients who have dysphagia, pneumopathy, or significant asthenia. Therefore, treatment in such patients must be administered under the control of a specialist and only if the benefit of treatment is considered to outweigh the risk.

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

Pre-existing neuromuscular disorders

Patients with pre-existing neuromuscular disorders such as myasthenia gravis, Eaton Lambert syndrome or amyotrophic lateral sclerosis may have an increased sensitivity to botulinum toxin, which may result in excessive muscle weakness. Therefore, botulinum toxin should only be used

with caution and under close medical supervision in such patients.

Bleeding disorders

As with any intramuscular injection, RELFYDESS should be used with caution in patients with prolonged bleeding times or bleeding disorders from any cause.

Pre-existing conditions at the injection site

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

Caution should be used when RELFYDESS treatment is used in patients who have marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.

Ophthalmic adverse reactions

Dry eye, reduced tear production, reduced blinking, and corneal disorders may occur with the use of botulinum toxins. If symptoms of dry eye (e.g., eye irritation, photophobia, or visual changes) persist, consider referring the patient to an ophthalmologist.

Antibody formation

Antibodies to botulinum toxin type A may develop during treatment with botulinum toxin. Some of the antibodies formed are neutralising which may lead to treatment failure of botulinum toxin type A (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

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.

Use in the elderly

There are no additional precautions regarding the use of RELFYDESS in the elderly population.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been conducted with RELFYDESS.

However, the potential for certain drugs as listed below to potentiate the effects of RELFYDESS warrants consideration given the potential risks involved and such drugs should be used with caution:

- Other botulinum toxin products
- Aminoglycosides or other agents interfering with neuromuscular transmission
- Anticholinergic drugs
- Muscle relaxants

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of RELFYDESS on human fertility is unknown. No animal fertility studies have been conducted with relabotulinumtoxinA. Intramuscular doses of 4 U/kg (males) and 8 U/kg (females) of a similar drug did not affect rat fertility. Decreased fertility occurred with higher doses, which also resulted in signs of toxicity. The relevance of these findings to human fertility is not known.

Use in pregnancy – Pregnancy Category B3

There are only limited data from the use of botulinum toxin type A in pregnant women.

RELFYDESS is not recommended during pregnancy and in women of childbearing potential not using contraception.

Category B3

No reproductive and developmental toxicity studies have been performed with relabotulinumtoxinA. However, adverse embryofetal development effects have been seen in rat and rabbit studies with other botulinum toxins (lower fetal weights, delayed ossification, abortions and embryofetal development lethality). These adverse embryofetal development effects occurred in the context of maternotoxicity. The potential risk for humans is unknown.

Use in lactation.

It is unknown if relabotulinumtoxinA is excreted in human milk. The excretion of relabotulinumtoxinA in milk has not been studied in animals. The use of RELFYDESS during lactation is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Other botulinum toxin products have been reported to have a minor or moderate influence on the ability to drive and/or use machines. There is a potential risk of localised muscle weakness or visual disturbances linked with the use of RELFYDESS which may temporarily impair the ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

The safety of RELFYDESS for the treatment of moderate to severe glabellar lines, moderate to severe lateral canthal lines and in combination was evaluated in three pivotal Phase 3 placebo-controlled clinical studies including 806 patients receiving RELFYDESS. Most adverse events reported were of mild to moderate severity. The most frequently reported related adverse events overall in all placebo-controlled studies for RELFYDESS (≥ 50 units)-treated patients were headache (4.3%), injection site pain (2.9%), injection site bruising (2.5%) and eyelid ptosis (1.6%).

Treatment emergent adverse events represent untoward changes in health irrespective of a causal association after exposure to a medicinal product. **Table 1** and **Table 2** present treatment-emergent adverse events occurring at an incidence of >1% in the pivotal Phase 3 placebo-controlled clinical studies, along with those subjects in the control groups.

Table 1: Moderate to severe glabellar lines - Number (%) of Subjects with Adverse Events (> 1% of Subjects)

System Organ Class / Preferred Term	RELFYDESS (N=338) n (%)	Placebo (N=133) n (%)
Subjects with any TEAE	31 (9.4)	7 (4.9)
Infections and infestations	**11 (3.3)**	**6 (4.2)**
Covid-19	9 (2.8)	6 (4.2)
Sinusitis	2 (0.6)	0
General disorders and administration site conditions	**4 (1.2)**	**1 (0.6)**
Injection site bruising	4 (1.2)	1 (0.6)
Nervous system disorders	**11 (3.3)**	**0**
Headache	11 (3.3)	0
Eye disorders	**5 (1.5)**	**0**
Eyelid ptosis	5 (1.5)	0

Table 2: Moderate to severe lateral canthal lines - Number (%) of Subjects with Adverse Events (> 1% of Subjects)

System Organ Class / Preferred Term	RELFYDESS (N=353) n (%)	Placebo (N=131) n (%)
Subjects with any TEAE	32 (9.0)	17 (13.5)
Infections and infestations	**13 (3.7)**	**10 (7.7)**
Covid-19	10 (2.9)	8 (6.0)
Sinusitis	4 (1.1)	2 (1.7)
General disorders and administration site conditions	**13 (3.6)**	**4 (3.2)**
Injection site bruising	13 (3.6)	4 (3.2)
Nervous system disorders	**4 (1.2)**	**2 (1.7)**
Headache	4 (1.2)	2 (1.7)
Investigations	**4 (1.1)**	**1 (0.9)**
Blood pressure increased	4 (1.1)	1 (0.9)

When glabellar lines and lateral canthal lines were treated in combination, the nature and frequency of adverse events were comparable to what was observed when patients were treated for the individual indications.

Adverse Reactions

The majority of adverse reactions reported with RELFYDESS in the pivotal placebo-controlled phase III trials after one injection were of mild to moderate intensity, occurred within the first month following injection, and were transient. The adverse reactions from this pool are presented in the tables below and are organized according to primary system organ class (SOC) and MedDRA preferred term.

Tabulated list of adverse reactions

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).

Moderate to severe glabellar lines

The following adverse reactions were observed in patients that were administered RELFYDESS for the temporary improvement in the appearance of moderate to severe glabellar lines

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Common	Headache
Eye disorders	Common	Eyelid ptosis
Skin and subcutaneous tissue disorders	Uncommon	Brow ptosis
Musculoskeletal and connective tissue disorders	Uncommon	Muscular weakness
General disorders and administration site conditions	Common	Injection site bruising

Moderate to severe lateral canthal lines

The following adverse reactions were observed in patients that were administered RELFYDESS for the temporary improvement in the appearance of moderate to severe lateral canthal lines.

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Common	Headache
Musculoskeletal and connective tissue disorders	Uncommon	Muscular weakness
General disorders and administration site conditions	Common	Injection site bruising
	Uncommon	Injection site pain

When glabellar lines and lateral canthal lines were treated in combination, the nature and frequency of adverse reactions were comparable to what was observed when patients were treated for the individual indications.

Description of adverse reactions

From clinical phase III placebo-controlled trials READY-1, READY-2 and READY-3

The mean time to onset for any adverse reaction after injection in any indication varied, ranging from 0 days (injection site pain) to 17 days (eyelid ptosis) in RELFYDESS exposed subjects and from 0 days (injection site pain) to 2.5 days (headache) in placebo subjects. The mean duration for any adverse reaction in any indication varied, ranging from 1 day (injection site pain) to 73.7 days (muscular weakness) in RELFYDESS exposed subjects and from 2.5 days (headache) to 8.6

days (injection site bruising) in placebo subjects. All the adverse reactions reported except one (headache) were of mild to moderate intensity.

No analysis of the adverse reactions pattern between various subgroups for the three different indications was deemed meaningful due to the limited incidence of adverse reactions. Also, the analysis of the incidence of the sum of single adverse reactions between the different subgroups from all three indications was of limited relevance for the same reason.

Risk of spread of toxin distant from the site of administration

No subject experienced a distant spread of toxin effect in the clinical development program.

Hypersensitivity reactions

Across all the placebo-controlled studies, one patient (0.12%) treated with ≥50 units RELFYDESS experienced a potential hypersensitivity event (injection site reaction) which was mild and localised.

Related TEAEs* (Injection site reactions)

In addition, related TEAEs concerning Injection site reactions in RELFYDESS treated subjects (receiving ≥50 units) in the "all placebo-controlled studies pool" were: Injection site pruritus, Swelling, Erythema, Discomfort, Haematoma, Hypersensitivity, and Warmth.
*Considered related by the investigator at the individual adverse event level

From open label long term safety study READY-4

Safety data from the open-label extension study is consistent with placebo-controlled safety data from READY-1, READY-2 and READY-3.

The most frequently reported adverse reactions in READY-4 were Injection site pain (7%), Injection site bruising (7%) and Headache (6%). There was no trend of increased incidence of adverse reactions in subjects who received up to 7 treatments. Most of the adverse reactions were classified as mild, with none classified as severe, and there was no change in the severity pattern of adverse reactions with repeat administration/treatment.

Risk of spread of toxin distant from the site of administration

No subject experienced a distant spread of toxin effect.

Hypersensitivity reactions

Potential hypersensitivity events were experienced by 4 subjects (0.4%). These were considered mild in intensity, began on the same day as the injection, resolved within 2 days, and were localised to the injection site.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Excessive doses may produce distant and profound neuromuscular paralysis. Overdose could lead to an increased risk of the botulinum toxin entering the bloodstream and may cause complications associated with the effects of oral botulinum poisoning. (e.g., dysphagia and

dysphonia).

Symptoms of overdose may not be present immediately post-injection. Should accidental injection or ingestion occur, the patient should be medically monitored for several weeks for any signs and/or symptoms of excessive muscle weakness or muscle paralysis.

Admission to hospital should be considered for patients with obvious symptoms of botulinum toxin overdose.

In the event of overdose, the patient should be medically monitored for any signs and/or symptoms of excessive muscle weakness or muscle paralysis. General supportive care is advised and symptomatic treatment should be instigated if necessary. Respiratory support may be required where excessive doses cause paralysis of the respiratory muscles.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The well-established mechanism of action of *Clostridium botulinum* type A neurotoxin products includes blocking the release of acetylcholine from the presynaptic cholinergic neuronal synapse to produce muscle relaxation. The heavy chain of botulinum toxin type A mediates attachment to the presynaptic surface of cholinergic neurons and internalisation of the bound toxin occurs by endocytosis. The catalytic light chain is then translocated across the vesicular membrane into the cytosol. The light chain is an enzyme that cleaves the synaptosome-associated protein of 25 kDa (SNAP-25) in the nerve terminals to block binding of acetylcholine vesicles with the cell membrane and prevent the release of acetylcholine from vesicles into the synapse. When injected intramuscularly, the toxin induces partial paralysis of the affected muscle which temporarily reduces muscle activity, leading to the transient reduction of glabellar lines or lateral canthal lines. Botulinum toxin type A products have a long duration of action in animals and humans measured in weeks to months. Muscle function will return gradually with regrowth of the nerve fibres with new nerve terminals (normally within 12 weeks) to innervate the muscles reversing the denervation by toxin administration.

Clinical trials

The data described below reflect results in the Phase III placebo-controlled studies READY-1, READY-2 and READY-3. A total of 1,012 patients were treated in 3 pivotal trials including 806 patients treated with RELFYDESS and 206 patients treated with placebo. There were also an additional 902 RELFYDESS-treated patients in an open-label long term safety study (READY-4).

Onset of action reported within 1 day (up to 39% and 34% in glabellar and lateral canthal lines, respectively), with a median time to onset of 2 to 3 days. An effect has been demonstrated for 6 months after injection.

Subject psychological function was observed using FACE-Q™ psychological function scale (which incorporates subject ratings on self-liking, feeling positive, feeling okay, feeling happy, comfort with self, self-acceptance, feeling good, feeling confident, feeling attractive and feeling great).

The FLTSQ scale (Facial Line Treatment Satisfaction Questionnaire) was used to observe subject satisfaction with GL and/or LCL appearance (which incorporated subjects ratings on feeling comfortable with some facial expressions or position, facial lines visibility, skin smoothness, looking youthful , looking great for one's age, looking relaxed, looking attractive, looking well-rested and looking renewed) but also to observe subject treatment satisfaction (by incorporating subject ratings on re-treatment, treatment recommendation, results expectations, naturalness, right treatment choice, treatment results happiness but also treatment outcome and treatment improvement satisfaction).

FACE-Q™ psychological function scale and FLSTQ scale responses indicated RELFYDESS-treated subjects showed improvement in psychological well-being and were more satisfied with their treatment and appearance than placebo subjects at all post-treatment time points. As assessed by FACE-Q™ and FLTSQ the positive psychological function and subject satisfaction were maintained for 6 months following treatment.

Patients receiving RELFYDESS (1699 in total) were tested for anti-drug antibody formation at baseline and following each treatment. No patients tested positive for toxin-neutralising antibodies.

Glabellar Lines (READY-1 and READY-3)

In two pivotal Phase III multi-centre, double-blind, placebo-controlled studies 451 patients were treated in GLs at the recommended dose of 50 units. READY-1 assessed RELFYDESS treatment of GL only; READY-3 assessed combination treatment of GL and LCL. Results for READY-3 are described for the patients receiving RELFYDESS in both the GL and LCL in combination.

Primary efficacy was the proportion of subjects who were responders, defined as achievement of a score of 0 or 1 in glabellar line severity on the GL-ILA 4-Point Photographic Scale (GL-Investigator Live Assessment) of Glabellar Line Severity at maximum frown at the Month 1 visit. The majority of subjects in both the RELFYDESS or placebo group had severe glabellar lines at baseline as determined by the investigator (74.5% and 75.8% respectively).

Treatment success for GL as measured by investigator (GL-ILA, using a 4-point scale [0=none, 1=mild, 2=moderate, 3=severe], at maximum frown) was statistically significantly greater ($p<0.001$) in the RELFYDESS group compared to the placebo group at 1 month (**Table 3**)

Table 3: Investigator Assessment of Glabellar Line Treatment Success[a] (% and Number of Subjects) at Month 1[b] in Double-blind, Placebo-Controlled Clinical Studies

Study	RELFYDESS 50 units GL	RELFYDESS 50 units GL and 60 units LCL	Placebo
READY-1, GL only	96.3% N=199	-	4.5% N=67
READY-3 LCL & GL treatment	94.3% N=106	96.3% N=108	1.8% N=55

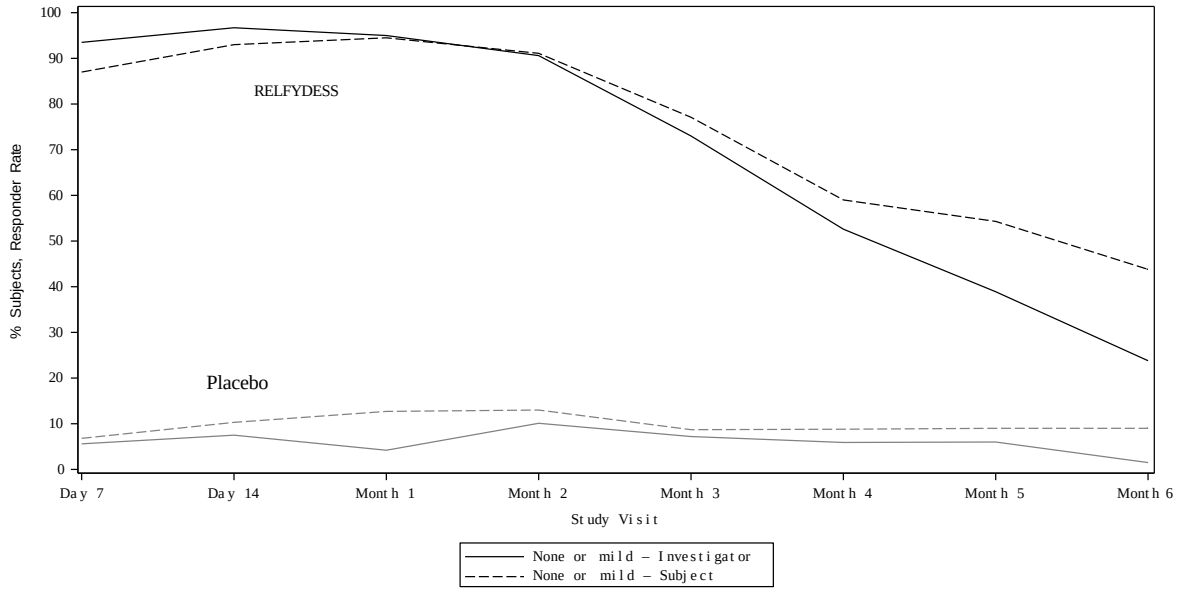
[a] achieved a score of 0 or 1 in GL severity on GL-ILA
[b] Day 30 primary efficacy endpoint; $p<0.001$

Subgroup analyses of the primary efficacy endpoint of responder rates based on the GL-ILA 4-Point Photographic Scale at maximum frown at Month 1 demonstrated the efficacy of RELFYDESS regardless of age, race, prior botulinum toxin use, or baseline severity score on the GL-ILA at maximum frown.

For subjects who achieved a score of 0 or 1 on both the GL-ILA 4-Point Photographic Scale and GL-SLA Static 4-Point Categorical Scale at maximum frown, the median number of days to a loss of a score of 0 or 1 was 168 days (24 weeks) in READY-1 and 140 days (20 weeks) in READY-3.

Investigator-assessed improvement in GL severity was displayed for 6 months in the RELFYDESS group compared to the placebo group (**Figure 3**).

Figure 3 RELFYDESS Investigator and Subject Assessed Glabellar Line Responder Rate (achieved a score of nonea or mildb in GL severity) Compared with Placebo Over Time (READY-1)



[a] score of none = 0
[b] score of mild = 1

When used in combined treatment with LCL, response (achieving 0 or 1 on the GL-ILA at maximum frown) was statistically significantly higher in RELFYDESS-GL/ RELFYDESS-LCL group compared with placebo GL/placebo LCL throughout the 6 months post-treatment.

Lateral Canthal Lines (READY-2 and READY-3)

In two pivotal Phase III multi-centre, double-blind, placebo-controlled studies 471 patients were treated in LCLs at the recommended dose of 60 units. READY-2 assessed RELFYDESS treatment of LCL only; READY-3 assessed combination treatment of GL and LCL. Results for READY-3 are described for the patients receiving RELFYDESS in both the GL and LCL in combination.

Primary efficacy was the proportion of subjects who were responders, defined as achievement of a score of 0 or 1 in lateral canthal line severity on the LCL-ILA 4-Point Photographic Scale (LCL-Investigator Live Assessment) of Lateral Canthal Line Severity at maximum smile, at the Month 1 visit. The majority of subjects in both the RELFYDESS or placebo group had severe bilaterally symmetrical lateral canthal lines at baseline as determined by the investigator (42.3% and 42.7% respectively).

Treatment success for LCL as measured by investigator (LCL-Investigator Live Assessment, using a 4-point scale [0=none, 1=mild, 2=moderate, 3=severe], at maximum smile) was statistically significantly greater ($p<0.001$) in the RELFYDESS group compared to the placebo

group at 1 month (**Table 4**).

Table 4: Investigator Assessment of Lateral Canthal Line Treatment Success[a] (% and Number of Subjects) at Month 1[b] in Double-blind, Placebo-Controlled Clinical Studies

Study	RELFYDESS 60 units LCL	RELFYDESS 60 units LCL & 50 Units GL	Placebo
READY-2, LCL only	87.2% N=204	-	11.9% N=69
READY-3, LCL & GL treatment	78.1% N=117	83.3% N=108	19.3% N=55

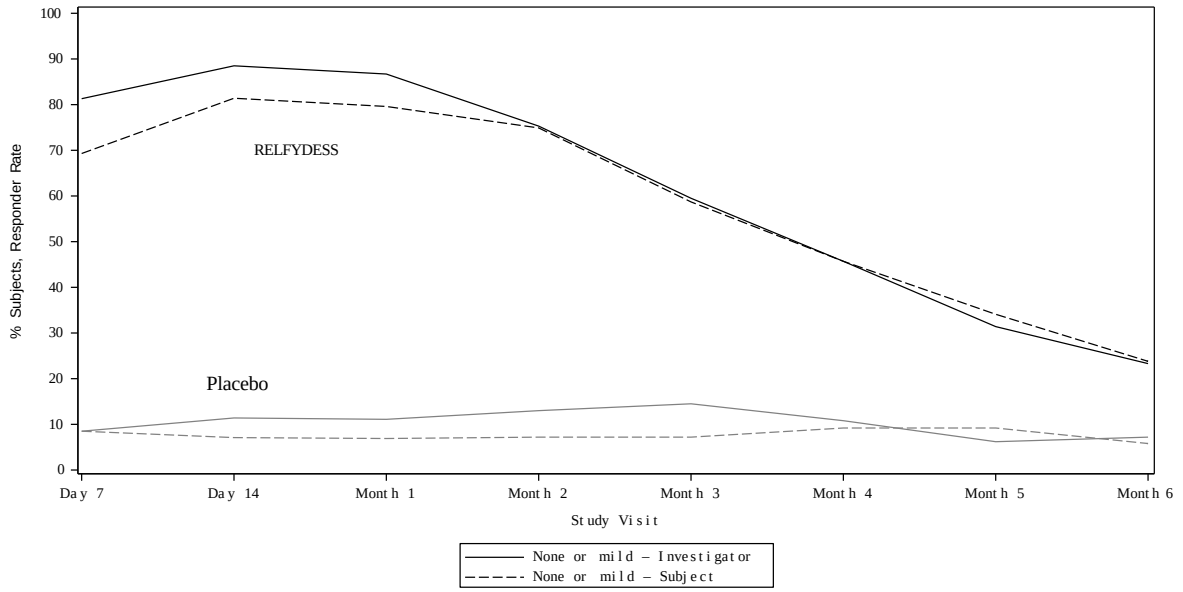
[a] achieved a score of 0 or 1 in LCL severity on LCL-ILA
[b] Day 30 primary efficacy endpoint; p<0.001

Subgroup analyses of the primary efficacy endpoint of responder rates based on the LCL-ILA 4 Point Photographic Scale at maximum smile at Month 1 demonstrated the efficacy of RELFYDESS regardless of age, race, prior botulinum toxin use, or baseline severity score on the LCL-ILA at maximum smile.

For subjects who achieved a score of 0 or 1 on both the LCL-ILA 4-Point Photographic Scale and LCL-SLA Static 4-Point Categorical Scale at maximum smile, the median number of days to a loss of a score of 0 or 1 in the RELFYDESS group was 144 (20.6 weeks) in the Lateral Canthal Lines Treatment Pool and 162 (23.1 weeks) in READY-2, 140 (20.0 weeks) in the GL placebo/LCL RELFYDESS group and 142 (20.3 weeks) in the GL RELFYDESS /LCL RELFYDESS group in READY-3.

Investigator and subject-assessed improvement in LCL severity was displayed for 6 months in the RELFYDESS group compared to the placebo group (**Figure 4**).

Figure 4: RELFYDESS Investigator and Subject Assessed Lateral Canthal Line Responder Rate (achieved a score of nonea or mildb in LCL severity) Compared with Placebo Over Time (READY-2)



[a] score of none = 0
[b] score of mild = 1

When used in combined treatment with GL, response (achieving 0 or 1 on the LCL-ILA at maximum smile) was statistically significantly higher in RELFYDESS GL/ RELFYDESS LCL group compared with placebo GL/placebo LCL at all post-treatment timepoints except month 6 (p=0.052).

Open Label Study (READY-4)

READY-4 was a Phase III, multicenter, open-label study to evaluate the safety of repeated injections of RELFYDESS for the long-term treatment of moderate-to-severe glabellar lines and lateral canthal lines (with at least 12 weeks in between treatment cycles).

In READY-4, RELFYDESS administration of up to 110 U and up to 7 GL and/or LCL treatments over a 52-week study period demonstrated favourable efficacy results in both glabellar lines and lateral canthal lines whether treated at the same time or independently.

5.2 PHARMACOKINETIC PROPERTIES

RELFYDESS is not expected to be present in the peripheral blood at measurable levels following intramuscular injection owing to the extremely small quantities administered and rapid irreversible binding to cholinergic nerve terminals. Pharmacokinetic studies have therefore not been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Other excipients are dibasic sodium phosphate dihydrate, monobasic sodium phosphate dihydrate, potassium chloride, sodium chloride, polysorbate 80, tryptophan, water for injections.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

12 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2-8°C. Refrigerate. Do not freeze. Keep vials in the outer carton in order to protect from light.

Unopened vial may be brought to room temperature at 25°C as the stability of RELFYDESS has been demonstrated for up to 24 hours at room temperature.

6.5 NATURE AND CONTENTS OF CONTAINER

RELFYDESS is supplied in 2 mL Type I glass vial, bromobutyl stopper and aluminium overseal with polypropylene flip-off top.

Each vial contains 150 units of botulinum toxin type A in 1.5 mL of solution.

Pack containing 1 or 10 vials of RELFYDESS 100 units/mL solution for injection.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Immediately after treatment of the patient, any residual RELFYDESS which may be present in either vial or syringe should be inactivated with dilute hypochlorite solution (1% available chlorine).

Spillage of RELFYDESS should be wiped up with an absorbent cloth soaked in dilute hypochlorite solution.

In Australia, any unused medicine 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.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Active substance is a purified botulinum toxin type A1 neurotoxin. The neurotoxin is a 150 kDa molecule consisting of two protein sub-units: a 100 kDa heavy chain and 50 kDa light chain. The two chains are connected by a disulfide bond between two cysteine residues.

CAS number

93384-43-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Ipsen Pty Ltd
Level 5, 627 Chapel Street
South Yarra VIC 3141

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Galderma Australia Pty Ltd
Level 18, 1 Denison Street
North Sydney NSW 2060

Telephone: 1800 800 765

9 DATE OF FIRST APPROVAL

To be completed upon approval

10 DATE OF REVISION

10.1 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	Not Applicable