▼ 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 https://www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – DAXXIFY®
(daxibotulinumtoxinA) Powder for injection

1 NAME OF THE MEDICINE

DAXXIFY® (daxibotulinumtoxinA) 100 Units sterile lyophilised powder for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of DAXXIFY powder for injection contains 100 Units of daxibotulinumtoxinA, histidine (0.14 mg), histidine hydrochloride monohydrate (0.65 mg), polysorbate 20 (0.1 mg), RTP004 peptide (11.7 mcg), and trehalose dihydrate (36 mg).

DaxibotulinumtoxinA is a 150 kDa botulinum toxin without accessory proteins purified from the bacterium *Clostridium botulinum* type A.

For the full list of excipients, see **section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Powder for Injection.

DAXXIFY is a white to off-white lyophilised powder in single-dose vial for reconstitution with sterile 0.9% Sodium Chloride Injection, USP.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DAXXIFY is indicated for:

- the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.
- the treatment of cervical dystonia in adult patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

DAXXIFY should only be administered by physicians with appropriate qualifications.

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

The potency units of DAXXIFY for injection are specific to the preparation and test method utilised.

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

DAXXIFY should be administered no more frequently than every three months. Consideration of the cumulative dose is necessary when treating adult patients with DAXXIFY. Physicians should be aware of whether patients are receiving treatment with other botulinum toxin products for other indications.

Preparation and Dilution Technique

DAXXIFY is supplied in single-dose 100 Unit vials. Prior to intramuscular injection, reconstitute each vial of DAXXIFY with the required amount of sterile 0.9% Sodium Chloride Injection, USP to obtain a reconstituted solution at the appropriate concentration described in Table 1.

Table 1. DAXXIFY 100 Unit Vials
Dilution Volume for Reconstitution

Indication	Diluent * Added to 100 Unit Vials	Resulting dose in Units per 0.1 mL
Glabellar Lines, Adults	1.2 mL	8 Units
Cervical Dystonia, Adults	1.0 mL 2.0 mL	10 Units 5 Units

* 0.9% Sodium Chloride Injection, USP

Slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Dispose of any unused diluent. Gently mix DAXXIFY with 0.9% Sodium Chloride Injection, USP by rotating the vial.

Reconstituted DAXXIFY solution is clear to slightly opalescent and colourless and free of particulate matter. Inspect visually the reconstituted DAXXIFY for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy or discoloured or contains flakes or particles.

Administer DAXXIFY within 72 hours after reconstitution. During this time period, store unused reconstituted DAXXIFY in a refrigerator between 2°C to 8°C and protected from light. Do not freeze reconstituted DAXXIFY. Dispose of any unused DAXXIFY.

Dosage for Glabellar Lines

The total recommended dose is 40 Units per treatment session divided into five equal intramuscular injections of 8 Units each (two injections in each corrugator muscle and one injection in the procerus muscle).

Duration of effect: up to 6 months, however, it may last longer or shorter in individual patients.

Time to first onset of effect: Median of two days after treatment with some subjects reporting onset as early as the day after treatment.

Method of Administration for Glabellar Lines

For intramuscular use.

After reconstitution, use each DAXXIFY vial for only one injection session and for only one patient. Discard any remaining solution in vial immediately after administration.

Because the exact location, size, and activity of the muscles can vary markedly among individuals, physicians administering DAXXIFY must understand the relevant anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and diseases. After assessment, the location of the corrugator muscle injection sites may need to be adjusted based on individual facial anatomy and the pattern of muscle contraction.

The upper eyelid margin position should be carefully examined for separation or weakness of the levator palpebrae superioris muscle. Evaluate the range of upper eyelid excursion while manually immobilising the frontalis to assess degree of levator function and frontalis compensation.

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

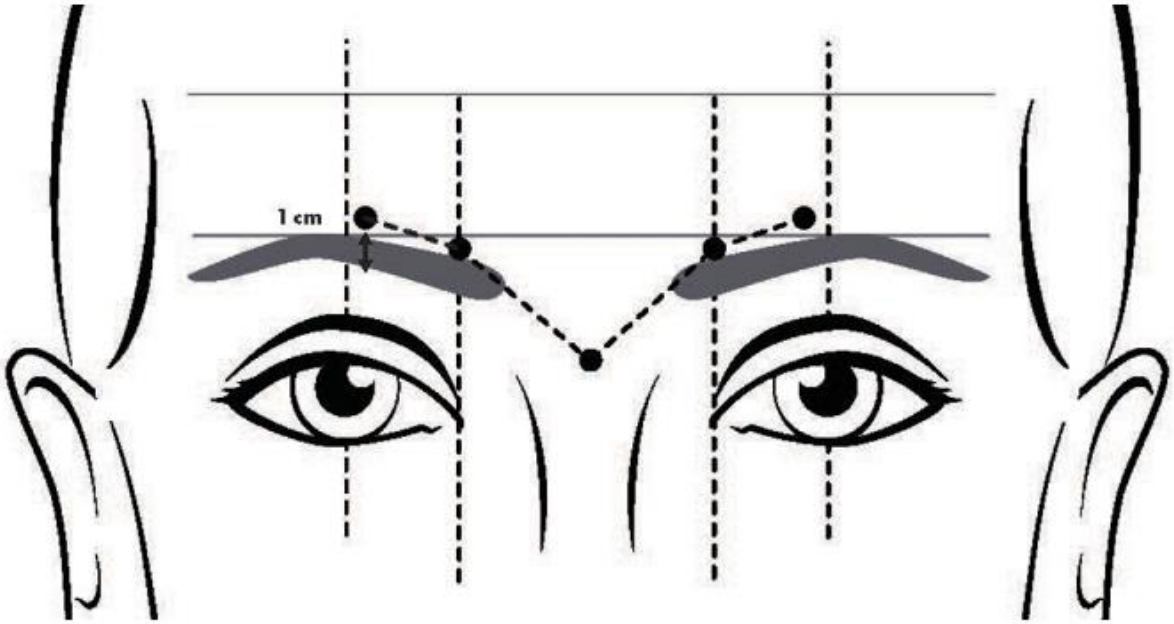
- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Ensure the injected volume/dose is accurate and administer in a steady, controlled manner.
- Do not inject DAXXIFY less than 1 centimetre above the bony superior orbital rim.

To inject DAXXIFY, clean the exposed portion of the stopper with an alcohol swab and aseptically withdraw at least 0.5 mL of the reconstituted solution from the vial into a sterile syringe. Replace the needle used to withdraw the product with a 30 to 33 gauge sterile needle for injection. Expel any air bubbles prior to administration.

Advance the needle through the skin into the underlying muscle while applying finger pressure on the superior medial orbital rim.

- Inject a dose of 8 Units (0.1 mL) into each of the 5 injection sites: 2 injections into medial corrugator and lateral corrugator muscles respectively, and 1 injection in the procerus muscle (Figure 1).

Figure 1. INJECTION SITES FOR GLABELLAR LINES



Dosage for Cervical Dystonia

Select dose based on severity of head and neck position and degree of muscle hypertrophy. In patients previously treated with another botulinum toxin, their prior dose, response to treatment, duration of effect, and adverse event history should be taken into consideration when determining the initial DAXXIFY dose. The initial dose of DAXXIFY in clinical studies for the treatment of cervical dystonia ranged from 125 Units to 250 Units given intramuscularly as a divided dose among affected muscles. A description of the average DAXXIFY dose and percentage of total dose injected into specific muscles in the pivotal clinical trials can be found in Section 5.1. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. The total dose administered in a single treatment is recommended to be between 125 Units and 250 Units.

Clinical studies with DAXXIFY in cervical dystonia suggest that the peak effect occurs between weeks 4 and 6 after injection.

Where dose modification is necessary for the treatment of cervical dystonia, the open-label repeat treatment safety study suggests that dose adjustment can be made in 50-75 Unit steps according to the individual patient's response.

4.3 CONTRAINDICATIONS

Hypersensitivity

DAXXIFY is contraindicated in patients with known hypersensitivity to DAXXIFY or any of the components in the DAXXIFY formulation.

Infection at Injection Site

DAXXIFY is contraindicated in the presence of infection at the proposed injection sites.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Spread of Toxin Effect

Post marketing safety data from other approved botulinum toxins suggest that botulinum toxin effects may be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin 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 can be life-threatening and there have been reports of death related to the spread of toxin effects. The risk of symptoms is greatest in children treated for spasticity, but symptoms can occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including upper limb spasticity in children and approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than the maximum recommended total dose. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory difficulties occur.

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of DAXXIFY are specific to the preparation and assay method utilised. They are not interchangeable with other preparation of botulinum toxin products therefore, Units of biological activity of DAXXIFY cannot be compared to or converted to Units of any other botulinum toxin products assessed with any other specific assay method [see **Chemical structure**].

Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received botulinum toxin injections for unapproved uses. In these cases, the adverse reactions may have resulted from the administration of botulinum toxin products to the site of injection and/or adjacent structures. In some cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of botulinum toxin products.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported for botulinum toxin products. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. If such a reaction occurs, discontinue further injection of DAXXIFY and immediately institute appropriate medical therapy. The use of DAXXIFY in patients with a known hypersensitivity to DAXXIFY or any of its formulation components could lead to a life-threatening allergic reaction. [see **section 4.3 Contraindications**]

Cardiovascular System

There have been reports following administration of botulinum toxins of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

Pre-Existing Neuromuscular Disorders

Monitor patients with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) for increased neuromuscular compromise following botulinum toxin treatment. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalised muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from typical doses of DAXXIFY.

Dysphagia and Breathing Difficulties

Treatment with botulinum toxin products, including DAXXIFY, can result in swallowing or breathing difficulties. These reactions can occur within hours to weeks after injection with botulinum toxin. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory mechanisms may be involved. [see **Serious Adverse Reactions with Unapproved Use**]

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin products. Dysphagia may persist for several months. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. Treatment with botulinum toxins, including DAXXIFY, may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post marketing reports from other botulinum toxin products of serious breathing difficulties, including respiratory failure.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders.

Pre-existing Conditions at the Injection Site

Use caution when administering DAXXIFY to patients with surgical alterations to the facial anatomy, marked facial asymmetry, excessive dermatochalasis, deep dermal scarring, inflammation at the injection site(s), or pre-existing eyelid or eyebrow ptosis, when excessive weakness or atrophy is present in the target muscles.

Ophthalmic Adverse Reactions

Dry eye has been reported with the use of botulinum toxin products in the treatment of glabellar lines. Reduced tear production, reduced blinking, and corneal disorders may occur

with use of botulinum toxins, including DAXXIFY. If symptoms of dry eye (e.g., eye irritation, photophobia, or visual changes) persist, consider referring patient to an ophthalmologist.

Use in the elderly

Glabellar Lines

Among the 406 subjects treated with DAXXIFY in the placebo-controlled clinical trials, 36 subjects were 65 years or older. There was no increase in the incidence of treatment-related adverse events in patients over 65 years treated with DAXXIFY.

Cervical Dystonia

Among the 255 patients treated with DAXXIFY in the placebo-controlled clinical trial, 83 patients were 65 years or older. There was no increase in the incidence of treatment-related adverse events in patients over 65 years treated with DAXXIFY. Clinical studies of DAXXIFY did not include sufficient numbers of patients aged 65 and older to determine whether they responded differently from younger patients.

Paediatric use

Safety and effectiveness of DAXXIFY in patients less than 18 years of age have not been established.

Effects on laboratory tests

There were no significant differences in routine laboratory variables between the placebo and DAXXIFY groups.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been conducted with DAXXIFY.

However, the potential for certain drugs to potentiate the effects of DAXXIFY warrant consideration given the potential risks involved and should be used with caution.

- Aminoglycosides or other agents interfering with neuromuscular transmission
- Anticholinergic drugs
- Botulinum neurotoxin products
- Muscle relaxants

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a fertility and early embryonic development study in rats, intramuscular administration of weekly doses (3, 10 or 20 Units/kg in males and 3, 10 or 30 Units/kg in females) starting 4 weeks prior to mating for males and 2 weeks prior to mating for females caused reduced fertility resulting in reductions in body weight gain and food intake. No effects on fertility were noted at 3 Units/kg in males or 10 Units/kg in females.

Use in pregnancy – Pregnancy Category B3

There are no available data on DAXXIFY use in pregnant women to evaluate for a drug-associated risk in pregnant women. In animal reproduction studies, intramuscular administration of daxibotulinumtoxinA during pregnancy resulted in adverse effects on fetal growth (decreased fetal body weight and skeletal ossification) at maternally toxic doses.

Intramuscular administration of daxibotulinumtoxinA (3, 10 or 30 Units/kg) to pregnant rats four times during the period of organogenesis (on gestation days 7, 10, 13, and 16) caused decreased fetal body weight and decreased fetal skeletal ossification at the highest dose, which was associated with maternal toxicity. No embryofetal developmental toxicity was noted at doses up to 10 Units/kg.

Intramuscular administration of daxibotulinumtoxinA (0.02, 0.1, 0.48 or 2.4 Units/kg/day) to pregnant rabbits during the period of organogenesis (total of 13 doses) resulted in maternal lethality at 2.4 Units/kg/day and significant decreased maternal body weight at 0.48 Units/kg/day. No embryofetal developmental toxicity was noted at doses up to 0.48 Units/kg/day.

In a pre-/postnatal development study in rats, intramuscular administration of daxibotulinumtoxinA (3, 8 or 15 Units/kg) on gestation day 7 and 14 and lactation day 4, 14 and 21 had no effects on gestation, parturition or development of offspring despite maternal toxicity (decreased maternal body weight gain) at all doses.

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

Use in lactation.

It is not known whether DAXXIFY is excreted into the breast milk. The use of DAXXIFY during lactation is not recommended.

No effects on offspring development were observed in rats (see Use in Pregnancy).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be advised that they should avoid driving a car or engaging in other potentially hazardous activities if they develop any unusual symptoms such as loss of strength, muscle weakness, blurred vision, or drooping eyelids.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common side effects from treatment with DAXXIFY are typically mild, usually occur within one to two weeks after injection and while generally transient, may have a duration of several weeks or months.

Glabellar Lines

In the two randomised, placebo-controlled, Phase 3 clinical trials that assess the use of DAXXIFY for the temporary improvement in the appearance of moderate to severe glabellar lines, GL-1 and GL-2, 406 subjects received a single dose treatment of 40 Units DAXXIFY and 203 subjects received placebo.

The most frequent adverse events are presented in Table 2.

Table 2. Most Common Adverse Events ≥1% and More Frequent than Placebo in Pooled Double-Blind, Placebo-Controlled Trials for Glabellar Lines

Adverse Events	**DAXXIFY 40 U N=406 n (%)**	**Placebo N=203 n (%)**
Any adverse event	100 (24.6%)	28 (13.8%)
Headache	37 (9.1%)	5 (2.5%)
Nasopharyngitis	17 (4.2%)	6 (3.0%)
Injection site pain	15 (3.7%)	8 (3.9%)
Upper respiratory tract infection	11 (2.7%)	3 (1.5%)
Eyelid ptosis	9 (2.2%)	0 (0%)
Influenza	6 (1.5%)	2 (1.0%)
Injection site erythema	5 (1.2%)	4 (2.0%)
Injection site oedema	5 (1.2%)	3 (1.5%)
Urinary tract infection	5 (1.2%)	0 (0%)
Prothrombin time prolonged	2 (0.5%)	3 (1.5%)

In an 84-week open label repeat-dose safety study in glabellar lines, 2691 subjects were treated with 40 Units of DAXXIFY. Of these, 2380 subjects received one treatment with DAXXIFY, 882 received two treatments with DAXXIFY and 568 subjects received three treatments with DAXXIFY. Adverse reactions were reported in 535 of the 2691 subjects (20%). The adverse reaction profile was similar to that reported in single dose trials.

Injection site reactions were the most common adverse reactions, reported in 9% of subjects [including injection site pain (4%) , injection site erythema (3%), injection site oedema (3%), injection site bruising (1%), injection site pruritus (1%), injection site papule (<1%)], followed by headache (6%), oedema (2%), erythema (2%) and eyelid ptosis in 1% of subjects. The incidence of these adverse reactions did not increase with multiple re-treatments.

Cervical Dystonia

In the randomised, placebo-controlled, Phase 3 clinical trial to assess the use of DAXXIFY for the treatment of cervical dystonia, 255 subjects received a dose of DAXXIFY (125 subjects were randomised to receive 125 Units and 130 subjects were randomised to receive 250 Units) and 46 subjects received placebo. Table 3 lists adverse reactions that occurred in ⩾5% of DAXXIFY treated subjects and more frequent than placebo. Of note, dysphagia occurred in 1.6% and 3.9% of subjects in the 125 Units and 250 Units dose groups, respectively.

Table 3. Most Common Adverse Reactions ≥2% and More Frequent than Placebo in the Phase 3 Double Blind, Placebo Controlled Clinical Trial for Cervical Dystonia

Adverse Reaction	DAXXIFY 125 Units N=125 n (%)	DAXXIFY 250 Units N=130 n (%)	Placebo N=46 n (%)
Headache	11 (9%)	9 (7%)	1 (2%)
Injection site pain	10 (8%)	7 (5%)	2 (4%)
Injection site erythema	6 (5%)	3 (2%)	1 (2%)
Muscular weakness	6 (5%)	3 (2%)	0 (0%)
Musculoskeletal pain	5 (4%)	5 (4%)	0 (0%)
Nasopharyngitis	4 (3%)	3 (2%)	0 (0%)
Arthralgia	3 (2%)	1 (1%)	0 (0%)
Upper respiratory tract infection	2 (2%)	7 (5%)	2 (4%)
Spinal pain	3 (2%)	4 (3%)	1 (2%)
Atrioventricular block first degree	2 (2%)	0 (0%)	0 (0%)
Urinary tract infection	3 (2%)	0 (0%)	0 (0%)
Dysphagia	2 (2%)	5 (4%)	0 (0%)

In a 52-week, open-label, repeat-dose safety study in cervical dystonia, 357 subjects (271 from the randomised trial, 86 newly enrolled) received up to 4 treatments with DAXXIFY. Of these, 28 subjects received one treatment with DAXXIFY, 95 subjects received two treatments, 169 received three treatments, and 65 received four treatments with DAXXIFY.

Adverse reactions were reported in 138 patients (20%).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of DAXXIFY.

Treatment with botulinum toxins may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin.

Glabellar Lines

Among 2786 subjects receiving up to 3 treatments with DAXXIFY in the phase 3 studies, a total of 20 (0.8%) subjects developed treatment-emergent binding antibodies to daxibotulinumtoxinA and 33 (1.2%) subjects developed treatment-emergent binding antibodies to RTP004 peptide, the 35 amino acid peptide excipient. No subjects developed neutralising antibodies to DAXXIFY.

Cervical Dystonia

Among the 382 subjects receiving up to 5 treatments with DAXXIFY in the Phase 3 studies, the incidence of anti DAXXIFY antibody formation was 1.8% to daxibotulinumtoxinA and 2.4% to RTP004 peptide, the 35 amino acid peptide excipient. Two subjects who had been previously treated with botulinum toxin tested positive for neutralising antibodies. Both subjects exhibited a clinical response to treatment in the open label study.

Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the PK, PD, safety, and/or effectiveness of DAXXIFY products is unknown.

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

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

Excessive doses of DAXXIFY may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of the respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms or excessive muscle weakness or muscle paralysis. [see **section 4.4 Pre-Existing Neuromuscular Disorders** and **Dysphagia and Breathing Difficulties**] Symptomatic treatment may be necessary.

Symptoms of overdose are not likely to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

DaxibotulinumtoxinA blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine as the heavy chain of botulinum toxin type A mediates attachment to the presynaptic surface of cholinergic neurons. When injected into skeletal muscle, daxibotulinumtoxinA is internalised into the nerve terminal, then the catalytic light chain translocates into the neuronal cytosol where it cleaves SNAP25, a protein necessary for synaptic vesicle membrane docking and subsequent release of acetylcholine. This produces a dose-dependent decrease of muscle function, usually manifest with 2-3 days. Recovery of activity is gradual and results from the degradation of neurotoxin light chain in the neurons with a contribution from the formation of axonal sprouts. Muscle reinnervation occurs, leading to a slow reversal of the pharmacological effects.

Clinical trials

Glabellar Lines

Two randomised, double-blind, multi-centre, placebo-controlled clinical trials, Studies GL-1 and GL-2, were conducted to evaluate DAXXIFY for use in the temporary improvement of moderate-to-severe glabellar lines in adults. The 2 trials enrolled a total of 609 subjects (≥18 years old) with glabellar lines of at least moderate severity at maximum frown. A total of 405 subjects were randomised and 406 were treated with 40 Units of DAXXIFY and 204 subjects were randomised and 203 were treated with an equal volume of placebo. Subjects were excluded if they had eyelid ptosis, deep dermal scarring, excessive dermatochalasis or an inability to lessen glabellar lines by physically spreading them apart. Enrolled subjects were 21 to 75 years old, with a mean age of 50 years, were predominantly female (87%) and Caucasian (86%). The total dose was delivered in 5 equally divided intramuscular injections of 8 Units each to specific sites in the glabellar (Figure 1). Subjects were followed for at least 24 weeks after treatment.

Efficacy was determined through the assessment by investigators and subjects of frown wrinkle severity at maximum frown using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The primary efficacy endpoint was defined as improvement of at least 2 points from baseline for both the investigator's and subject's assessment and achieving a score of 0 or 1 (none or mild) at Week 4. The percentages of subjects who met the primary endpoint at Week 4 are presented in Table 4.

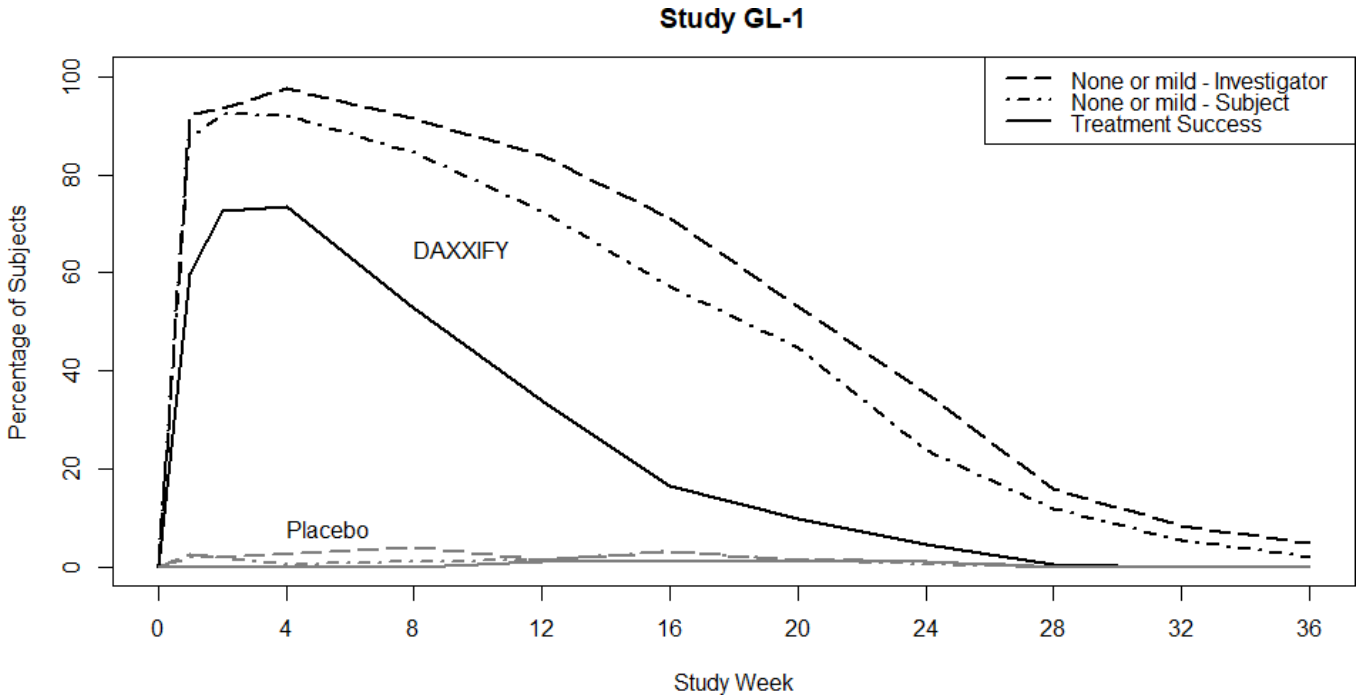
Table 4. Percentage of Subjects Achieving a Score of None or Mild and > 2-Grade Improvement from Baseline on the Investigator and Subject Assessment of Glabellar Line Severity at Maximum Frown at Week 4

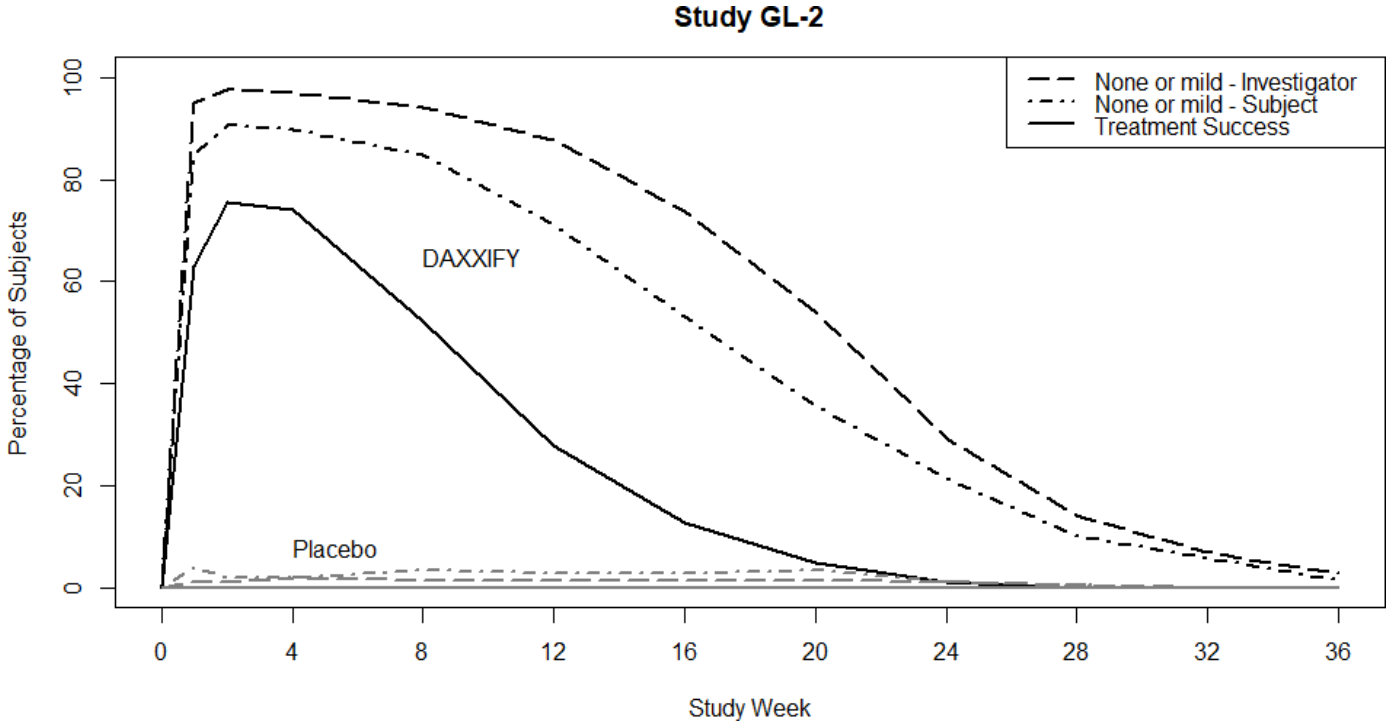
	STUDY GL-1			STUDY GL-2		
	DAXXIFY (N=201) n (%)	Placebo (N=102) n (%)	Treatment Difference and 95% Confidence Interval	DAXXIFY (N=205) n (%)	Placebo (N=101) n (%)	Treatment Difference and 95% Confidence Interval
Met Primary Endpoint[a]	148 (74%)	0 (0%)	74% (68%, 80%)	152 (74%)	0 (0%)	74% (68%, 80%)
Individual Components						
Investigator Assessment	172 (86%)	1 (1%)	---	187 (92%)	2 (2%)	---
Subject Assessment	152 (76%)	0	---	156 (77%)	0	---

[a] A score of 0 or 1 (none or mild) and ≥ 2-Grade Improvement from Baseline on both the Investigator and Subject Assessment

Subjects reported onset of effect as early as one day after treatment, with a median of two days. Figure 2 shows the proportion of subjects, over 36 weeks, rated as 0 or 1 (none or mild) by the investigator, 0 or 1 by the subject, and 0 or 1 with at least a 2-point improvement from their baseline based on both the investigator and subject ratings. Subjects were followed through at least Week 24 and then were discontinued from the study when both the investigator and subject scores returned to baseline. Subjects who returned to baseline levels prior to Week 36 were counted as non-responders following study discontinuation. For both Study GL-1 and Study GL-2, the median time to return to moderate or severe glabellar lines on both IGA-FWS and PFWS was 168 days (24 weeks).

Figure 2. Proportion of subjects rated as 0 or 1 (none or mild) by investigator, 0 or 1 by the subject in Study GL-1 and Study GL-2.





Cervical Dystonia

DAXXIFY has been investigated in a randomised, double-blind, placebo-controlled, multicentre trial in a total of 301 subjects. Subjects had a clinical diagnosis of cervical dystonia with baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score ⩾ 20, TWSTRS severity score ⩾15, TWSTRS disability score ⩾3, and TWSTRS pain score ⩾1. For subjects who had previously received a botulinum toxin treatment for cervical dystonia, the trial required that ⩾14 weeks had passed since the most recent botulinum toxin administration.

Subjects were randomised (3:3:1) to receive a single administration of DAXXIFY 125 Units (n=125), DAXXIFY 250 Units (n=130), or placebo (n=46). Each subject received 2.5 mL of reconstituted study agent divided amongst the affected muscles as selected by the investigator. Table 5 indicates the treated muscles along with the number of subjects treated and DAXXIFY units.

Table 5. Summary of Muscles Treated In Each DAXXIFY Treatment Group

Unilateral Muscle Injected	**DAXXIFY 125 Units**		**DAXXIFY 250 Units**	
	Number of Patients	**Median Units (min, max)**	**Number of Patients**	**Median Units (min, max)**
Levator Scapulae	106	20 (10, 30)	105	50 (20, 60)
Longissimus Capitis and Cervices	45	15 (10, 30)	58	40 (20, 60)
Scalenus Complex	55	15 (10, 15)	44	30 (20, 30)
Splenius Capitis	120	25 (10, 50)	127	50 (20, 100)
Splenius Cervices	65	20 (10, 50)	71	40 (20, 100)
Sternocleidomastoid	115	25 (10, 25)	121	50 (20, 50)
Trapezius	105	20 (15, 40)	105	40 (30, 80)

The mean age of study subjects was 58 years, and 65% of the subjects were women. At study baseline, 84% of subjects had previously received a botulinum toxin as treatment for cervical dystonia. The study was completed by 97% of study subjects.

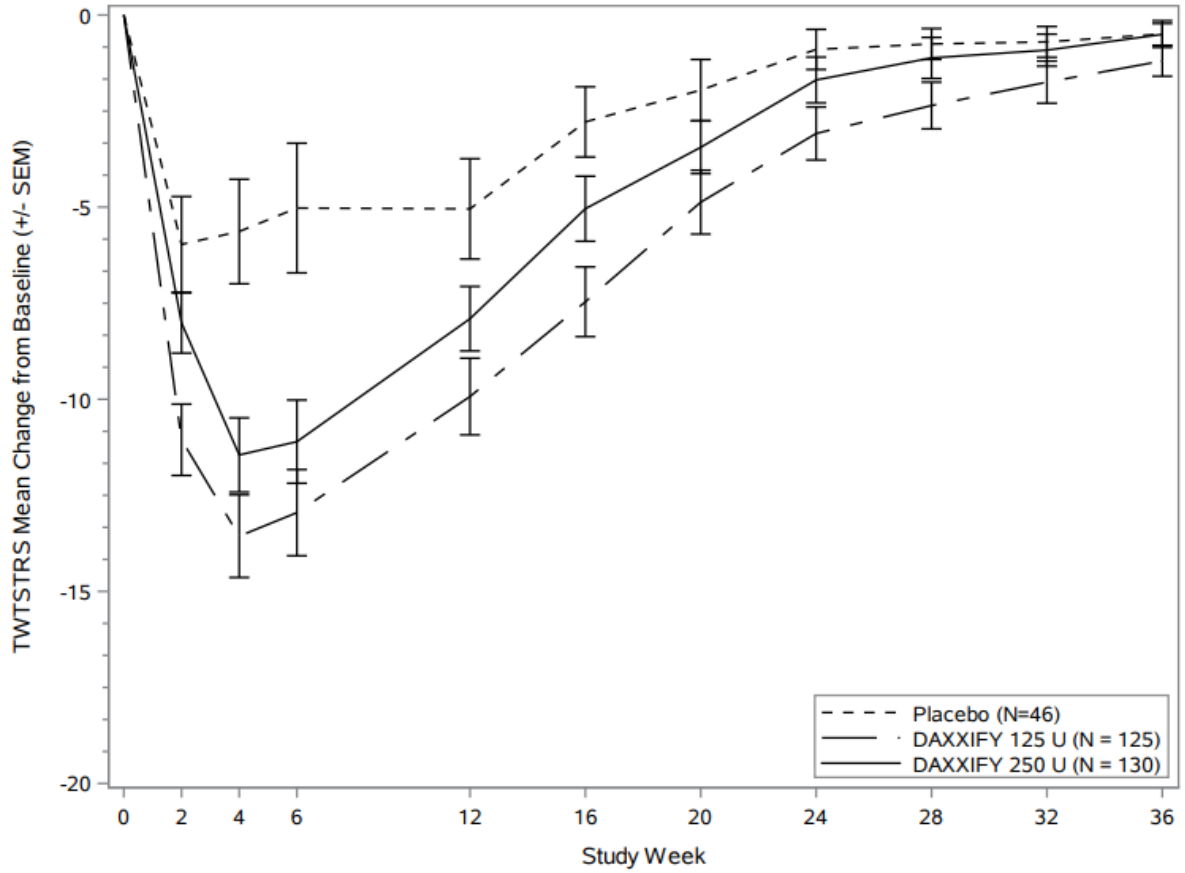
The primary efficacy endpoint was the mean change in the TWSTRS total score from baseline averaged over weeks 4 and 6. TWSTRS evaluates the severity of dystonia, patient-perceived disability from dystonia, and pain, with a range of possible scores from 0 to 85. The mean change from baseline in the total TWSTRS score was significantly greater for both dosage groups of DAXXIFY than for placebo (Table 6).

TABLE 6. Change in TWSTRS Score Averaged over Weeks 4 and 6 in Patients with Cervical Dystonia

TWSTRS Assessment	**Placebo (N = 46)**	**DAXI 125 Units (N = 125)**	**DAXI 250 Units (N = 130)**
Baseline mean	45.3	43.1	42.6
Least squares mean change from baseline	-4.3	-12.7	-10.9
Least squares mean difference from placebo (95% CI)		-8.4 (-12.2, -4.6)	-6.6 (-10.4, -2.8)
p-value		<0.0001	0.0007

A similar pattern of significant improvement versus placebo was observed in the clinician global impression of change (CGIC) and patient global impression of change (PGIC) scales, as well as the TWSTRS subscales of pain, severity and disability. The median time to return to pre-treatment status (i.e., time to loss of 80% of peak effect) was 20 to 24 weeks across the two treatment groups. Improvement from baseline at each study visit is shown in Figure 3.

Figure 3. Change from Baseline in TWSTRS-Total Score Over Time by Treatment Group. Error Bars are Standard Error of the Mean. Subjects Who Exit the Study are Imputed with Baseline.



5.2 PHARMACOKINETIC PROPERTIES

Using currently available analytical technology, it is not possible to detect DAXXIFY in the peripheral blood following intramuscular injection at the recommended dose.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted for daxibotulinumtoxinA.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of daxibotulinumtoxinA.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine (0.14 mg)

Histidine hydrochloride monohydrate (0.65 mg)

Polysorbate 20 (0.1 mg)

RTP004 peptide (11.7 mcg)

Trehalose dihydrate (36 mg)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Unopened vial

36 Months

Reconstituted solution

72 hours

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vial

Unopened DAXXIFY vials should be stored at room temperature 20°C to 25°C or refrigerated at 2°C to 8° in the original carton to protect from light.

Reconstituted solution

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C and protected from light for not more than 72 hours. Do not freeze reconstituted DAXXIFY. Dispose of any unused DAXXIFY.

6.5 NATURE AND CONTENTS OF CONTAINER

DAXXIFY (daxibotulinumtoxinA) for injection is a sterile lyophilised powder supplied in a single-dose vial containing 100 Units per vial.

Each carton contains 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

DaxibotulinumtoxinA is an acetylcholine release inhibitor and neuromuscular blocking agent. DaxibotulinumtoxinA is a 150 kDa botulinum toxin type A without accessory proteins purified from the bacterium Clostridium botulinum.

CAS number

93384-43-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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Carlton South VIC 3053,
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9 DATE OF FIRST APPROVAL

17 December 2024

10 DATE OF REVISION

24 June 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Update details of sponsor and distributor
Version number	Updated to 2.0 for version control and tracking purposes