DYSPORT: PRODUCT INFORMATION

NAME OF THE MEDICINE:-
Clostridium botulinum type A toxin-haemagglutinin complex

DESCRIPTION:-
Dysport Powder for Injection contains 125U, 300 or 500 IPSEN UNITS* per vial of Clostridium botulinum type A toxin-haemagglutinin complex, 125 microgram human serum albumin and 2.5 mg lactose in a sterile, lyophilised form without a preservative.

*One Ipsen unit (U) is defined as the median lethal intra-peritoneal dose (LD50) in mice of the reconstituted Dysport Powder for Injection.

ONE IPSEN UNIT is not equivalent to ONE UNIT of any other botulinum toxin preparation. From now on in this Product Information the term Ipsen unit will simply be replaced by the term unit.

Clostridium botulinum type A toxin-haemagglutinin complex has a molecular weight of about 900,000D and is a complex of proteins.

PHARMACOLOGY:-

Pharmacodynamics:

Clostridium botulinum type A toxin-haemagglutinin complex blocks peripheral cholinergic transmission at the neuromuscular junction by a presynaptic action at a site proximal to the release of acetylcholine. The toxin acts within the nerve ending to antagonise those events that are triggered by Ca$^{2+}$ which culminate in transmitter release. It does not affect postganglionic cholinergic transmission or postganglionic sympathetic transmission.

The action of toxin involves an initial binding step whereby the toxin attaches rapidly and avidly to the presynaptic nerve membrane. Secondly, there is an internalisation step in which toxin crosses the presynaptic membrane, without causing onset of paralysis. Finally the toxin inhibits the release of acetylcholine by disrupting the Ca$^{2+}$ mediated acetylcholine release mechanism, thereby diminishing the endplate potential and causing paralysis.

Recovery of impulse transmission occurs gradually as new nerve terminals sprout and contact is made with the postsynaptic motor endplate, a process which takes 6 - 8 weeks in the experimental animal.

Pharmacokinetics:

Pharmacokinetics have not been formally studied in humans or animals. Following intramuscular injection to man, there is usually a delay of 2-3 days with a peak effect between 10 and 21 days after injection. The duration of response varies but on average is 8-12 weeks.

CLINICAL TRIALS:-

Spasticity of the upper limb post-stroke in adults
In a dose-finding study (n=82) conducted in 11 European centres (6 in the UK, 4 in Germany and 1 in Austria), doses of 500 units (n=22), 1000 units (n=22) and 1500 units (n=19) of Dysport were compared with placebo (n=19) in a randomised, double blind, parallel group study in male and female patients aged 18 years or over with upper limb spasticity following a stroke. All doses of Dysport studied showed a significant reduction in spasticity measured by Modified Ashworth Scale (MAS) at week 4 compared with placebo. The MAS was also significantly reduced for all Dysport doses over 16 weeks in the elbow and wrist areas, and...
also for the fingers in the 1000 unit Dysport group (p<0.05). The number of patients who showed a response (reduction in MAS of at least 1 point on the timepoint scale) in at least 2 of the joint areas studied was significantly higher in the 500 units and 1000 units Dysport groups compared with placebo. Effects on function and range of movement for Dysport and placebo were not statistically different. A dose of 1000 units was considered optimal based on the results of this study.

In a placebo-controlled study (n=59) performed in 7 European centres (3 in the UK, 1 in Ireland and 3 in Germany), Dysport (1000 units; n=27) was compared with placebo (n=32) in a randomised, double-blind study in male and female patients aged over the legal age of consent with upper limb spasticity following a stroke. The best improvement in spasticity of elbow, wrist and finger joints as measured by the MAS was significantly better in Dysport treated patients than the placebo group (p=0.004). The magnitude of benefit in MAS score over the 16 week study period was also significantly higher in Dysport treated patients in the wrist (p=0.004) and finger joints (p=0.001) when compared to the placebo group. Passive range of movement over the 16 week study period in the elbow was marginally but significantly improved in Dysport treated patients compared to placebo (p=0.036).

The Modified Ashworth Scale (MAS) is the most commonly used measure of efficacy in the reduction of upper limb spasticity and is a direct measure of the degree of spasticity. The MAS assessment of spasticity involves separate assessment of the muscle tone of the elbow, wrist and fingers. The investigator or an appropriate delegate (e.g. physiotherapist) assesses the resistance encountered to passive movement at each joint on a six-point scale as follows:

0 = No increase in muscle tone.
1 = Slight increase in muscle tone, manifested by a catch and release, or by minimal resistance at the end of the range of motion when the affected part is moved in flexion or extension.
1+ = Slight increase in muscle tone, manifested by a catch, or by minimal resistance throughout the remainder (<1/2) of the range of movement (ROM).
2 = More marked increase in muscle tone through most of ROM, but affected part easily moved.
3 = Considerable increase in muscle tone, passive movement difficult.
4 = Affected part rigid in flexion or extension.

**Spasmodic torticollis in adults**

In a dose-finding study (n=74) conducted in 5 neurology clinics in Germany, doses of 250 units (n=19), 500 units (n=17) and 1000 units (n=18) of Dysport were compared with placebo (n=20) in a randomised, parallel group study in male and female patients aged 18 years or over with rotational torticollis. Improvements in symptoms were statistically significantly better than placebo for the 500 unit and 1000 unit dose groups at 4 weeks using Tsui score. A dose relationship was also demonstrated by patient and investigator assessments of improvement since injection. Compared with placebo, statistically significant differences were observed at 8 weeks for the 500 unit and the 1000 unit treatment groups but at 4 weeks only the comparisons of the 250 unit and the 1000 unit groups were statistically significant. Associated with an increase in dose is an increased risk, particularly of dysphagia and therefore the optimal initial dose appears to be 250-500 units. A dose range of 250-1000 units is appropriate for simple rotational torticollis.

In a double blind study (n=73) conducted in 7 centres in Sweden and Finland in male or female patients over the legal age of consent where Dysport (n=38) was compared with the other botulinum toxin preparation available in Australia, a ratio of approximately 3 units of Dysport was found to achieve similar effects to one unit of Botox for the treatment of spasmodic torticollis within the therapeutic dose range (250 to 1000 units).

**Dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older**
In a dose-finding study (n=125), doses of 10 units/kg (n=36), 20 units/kg (n=28) and 30 units/kg (n=30) of Dysport were compared with placebo (n=31) in a randomised, double-blind study conducted in 12 centres, (6 in the UK, 1 in Ireland and 5 in Poland) in patients aged 2-9 years with dynamic equinus spasticity. Study medication was administered by IM injection to the gastrocnemius muscle of both legs. Assessments were made at 4, 8 and 16 weeks post-treatment. At week 4 all doses of Dysport significantly reduced the dynamic component compared to placebo and the 20 units/kg group produced the greatest reduction (p=0.009). Improvement in dynamic component was due to increased muscle length during gait.

A double-blind placebo-controlled study was conducted in 40 patients aged 2-16 years in 1 centre in the UK with dynamic equinus spasticity, randomised to receive Dysport (n=22) or placebo (n=18). The dose was titrated according to individual clinical status. The mean Dysport dose for diplegics was 25 ± 3 units/kg (range 18-32) and for hemiplegics 16 ± 4 units/kg (range 11-25). The study demonstrated that at week 6 the initial foot contact was significantly better for Dysport (p<0.001) than placebo and this difference was still evident at 12 weeks. A further double-blind placebo-controlled study was conducted in 52 patients with dynamic equinus spasticity, randomised to receive Dysport 30 units/kg (n=26) or placebo (n=26). At week 16 there was a significant improvement in foot contact for the Dysport group (p=0.004). The degree of improvement was less than that seen in the study mentioned previously but this may be due to the difference in severity of dynamic equinus spasticity between the two studies.

**Blepharospasm and hemifacial spasm in adults**

A Phase II, multi-centre, randomized, double-blind, parallel group, placebo-controlled study (Study Y-47-52125-706) has been conducted to assess the efficacy and safety of a single administration, in 6 injection sites by subcutaneous injection, of three doses of Dysport (40U / eye, 80U / eye, 120U / eye) for the treatment of benign essential blepharospasm. Results of this study support a recommended starting dose of 40 units per eye, increasing to 80 units per eye where a sustained effect is required.

In open label, uncontrolled studies from the published literature, the treatment of hemifacial spasm was generally the same as for the treatment of unilateral blepharospasm.

The studies showed that visual function improved in the majority of cases, returning to normal or near to normal. Injection of Dysport abolished or reduced muscle spasm in patients with blepharospasm or hemifacial spasm, for whom a benefit was reported in 70-100% of the cases according to the investigator. Discomfort was also reduced, and the patients’ facial appearance improved.

Criteria for assessment of results varied from one study to another. However, the assessment techniques were mainly qualitative and subjective, relying on a nominal scale which takes into account criteria such as visual function, frequency of spasm or severity of spasm. Neither the severity of the illness, the length of time it existed before commencement of Dysport injections, nor the gender or age of the patient influenced response to treatment.

Despite the variety of doses and administration techniques reported in the published studies, the overall response profile was favourable across the studies. Following the initial treatment, substantial improvements were reported for both blepharospasm (success rate range: 77-100%) and hemifacial spasm (success rate range: 75-100%).

The onset of improvement post the initial injection varied from 1 day to 3 weeks for blepharospasm and from 2 to 7 days for hemifacial spasm. The duration of effect lasted between 5 and 24 weeks for blepharospasm and between 6 and 24 weeks for hemifacial spasm. The issue of time to peak effect post initial injection was assessed somewhat loosely in only about four of the submitted publications and the latter appeared to range from 3 days to 6 weeks and from 1 week to 6 weeks respectively for blepharospasm and hemifacial spasm.
There was a tendency for repeat injection to produce a comparable level of efficacy to the initial injection for both conditions.

There are no satisfactory efficacy and safety data on the use of Dysport for the treatment of blepharospasm and hemifacial spasm in children and adolescents younger than 18 years of age.

**Glabellar Lines**

During the clinical development of Dysport for the treatment of glabellar lines, more than 2600 patients were included in the different clinical trials.

In glabellar lines clinical studies, 1907 patients with moderate to severe glabellar lines have been treated at the recommended dose of 50 Units. Of these, 305 were treated with 50U in two Phase III double-blind placebo-controlled studies (Y-97-52120-718 and Y-97-52120-719) and 1200 treated with 50U in a long-term open-label repeated dose Phase III study (Y-97-52120-720).

The median time to onset of response was 2 to 3 days following treatment.

The maximum effect on the number of responders was observed at day thirty following injection, when 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) of placebo-treated patients. The patient's own assessment at maximum frown after thirty days gave a response rate of 82% (251/305) for those treated with Dysport and 6% (9/153) for those treated with placebo.

In both placebo-controlled phase III studies, Dysport injections significantly reduced the severity of glabellar lines for up to 4 months. In one of these two studies, the effect was still statistically significant (p<0.001) at 5 months with 17% (32/190) of patients treated with Dysport still responding to treatment compared to 1% (1/92) of placebo treated patients. In the other study the corresponding effect after 4 months (p=0.002) was 24% (24/99) vs. 4% (2/49) with no statistically significant difference beyond 4 months.

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). In patients who were rated 'moderate' or 'severe' as baseline, the responder rate at rest over repeated dose cycles was also consistent with the single dose studies, with ~70% of Dysport-treated patients considered by investigators to be responders thirty days after treatment.

**INDICATIONS:-**

For the treatment of
- spasticity of the upper limb in adults following a stroke
- spasmodic torticollis in adults
- dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older
- blepharospasm in adults
- hemifacial spasm in adults
- moderate to severe glabellar lines in adults

**CONTRAINDICATIONS:-**

Dysport is contra-indicated in individuals with known hypersensitivity to any component of Dysport.
Dysport is contra-indicated in patients diagnosed with myasthenia gravis or with Eaton-Lambert (myasthenic) syndrome.

Dysport is contra-indicated in the presence of any signs of infection at the proposed injection site.

**PRECAUTIONS:**

The recommended dosages and frequencies of administration for Dysport should not be exceeded. Extensive or inappropriate doses outside the recommended dosage range may lead to an increased risk of adverse effects.

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported. Patients treated with therapeutic doses may present excessive muscle weakness. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose and by not exceeding the recommended dose.

Dysport should be administered with caution to patients with existing problems in swallowing or breathing as these problems can worsen following the distribution of the effects of toxin into the relevant muscles. Aspiration has occurred in rare cases and is a risk when treating patients who have a chronic respiratory disorder.

Very rare cases of death, occasionally in the context of dysphagia, pneumopathy and/or in patients with significant asthenia have been reported after treatment with botulinum toxin type A or B. Patients with disorders resulting in defective neuro-muscular transmission, difficulty in swallowing or breathing are more at risk of experiencing these effects. In these patients, treatment must be administered under the control of a specialist and only if the benefit of treatment outweighs the risk. Patients and their care-givers must be warned of the necessity of immediate medical treatment in case of problems with swallowing, speech or respiratory disorders.

Dysport should only be used with extreme caution and under close supervision in patients with sub-clinical or clinical evidence of any defect in neuromuscular transmission (e.g. drug-induced neuromuscular weakness [see Interaction with other Medicines] or undiagnosed myasthenic syndromes). Such patients may have an increased sensitivity to agents such as Dysport, which may result in excessive muscle weakness. Dysport is not recommended for use in any patients suffering from any of the motor neurone disorders e.g. amyotrophic lateral sclerosis.

There are no reports of any immune response after the local administration of *Clostridium botulinum* type A toxin-haemagglutinin complex in accordance with doses recommended when treating hemifacial spasm. Antibody formation to botulinum toxin has been noted rarely in patients receiving Dysport. The principal risk factors for the formation of neutralizing antibodies after Dysport treatment are high doses (> 600 units per treatment), short intervals (< 3 months) between injections and booster injections (within the first month of treatment). Clinically, neutralising antibodies might be suspected by substantial deterioration in response to therapy and/or the need for consistent use of increased doses. The rate of formation of neutralizing antibodies in patients treated for glabellar lines has not been studied.

As with any intramuscular injection, Dysport should be used only where strictly necessary and with due caution in patients with prolonged bleeding times. The same caution applies where there are signs of inflammation at the proposed injection site. In this case, infection must be ruled out (see Contraindications).

It is essential to study the patient’s facial anatomy prior to administering Dysport for correction of moderate to severe glabellar lines. Facial asymmetry, ptosis, excessive
dermatochalasis, scarring and any alterations to this anatomy as a result of previous surgical interventions should be taken into consideration.

This product contains a small amount of human albumin. The risk of transmission of viral infection or prion-related infection such as Creutzfeldt-Jakob disease (CJD) cannot be excluded with absolute certainty following the use of human blood or blood products.

Serious and/or immediate hypersensitivity reactions have been rarely reported. As with all biological products, adrenaline and other precautions as necessary should be available for immediate administration should an anaphylactic reaction occur.

As with any injection, procedure-related injury could occur. An injection could result in localized infection, pain, inflammation, paraesthesia, hypesthesia, tenderness, swelling, erythema and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension etc. Care should be taken when injecting near vulnerable anatomic structures.

DUE TO THE LACK OF AN INTERNATIONAL UNIT, DYSPORT IS NOT THERAPEUTICALLY EQUIVALENT TO ANY OTHER BOTULINUM TYPE A TOXIN PREPARATION CURRENTLY AVAILABLE ON THE AUSTRALIAN MARKET. THE POTENCIES OF DYSPORT AND ANY OTHER BOTULINUM TYPE A TOXIN PREPARATION ARE BASED ON DIFFERENT ASSAY METHODS. IN VIEW OF THIS LACK OF HARMONISATION OF UNIT SYSTEMS FOR THE BOTULINUM TYPE A TOXINS ON THE MARKET, EXTREME CAUTION IS REQUIRED IF IT SHOULD PROVE NECESSARY TO SUBSTITUTE THE BOTULINUM TYPE A TOXIN OF ONE PHARMACEUTICAL COMPANY BY ANOTHER. THE EFFECT OF ADMINISTERING DIFFERENT BOTULINUM NEUROTOXIN SEROTYPES AT THE SAME TIME OR WITHIN SEVERAL MONTHS OF EACH OTHER IS UNKNOWN. EXCESSIVE NEUROMUSCULAR WEAKNESS MAY BE EXACERBATED BY ADMINISTRATION OF ANOTHER BOTULINUM TOXIN PRIOR TO THE RESOLUTION OF THE EFFECTS OF A PREVIOUSLY ADMINISTERED BOTULINUM TOXIN.

Effects on fertility
Fertility in rats was decreased at intramuscular doses of Clostridium botulinum type A toxin-haemagglutinin complex of 33 units per kg per week in males and 80 units per kg per week in females, due to reduced mating secondary to muscle paralysis.

Use in pregnancy – (Category B3)
There are limited data from the use of Dysport in pregnant women. There was no evidence of teratogenicity in rats and rabbits given Clostridium botulinum type A toxin-haemagglutinin complex during the period of organogenesis at respective doses up to 50 and 12 units per kg by daily or weekly intramuscular injection. Maternal toxicity and implantation losses were observed at high doses in both species. Intramuscular administration of Clostridium botulinum type A toxin-haemagglutinin complex to rats during gestation and lactation was associated with slightly reduced pup birth weight and weight gain at severe maternotoxic doses (50 units per kg). Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofetal development, parturition or postnatal development other than at doses causing maternal toxicity.

Dysport should be used during pregnancy only if the benefit justifies any potential risk to the fetus. Caution should be exercised when prescribing to pregnant women.

Use in lactation
It is not known whether Clostridium botulinum type A toxin-haemagglutinin complex is excreted in human or animal milk. The use of Dysport during lactation cannot be recommended.
Use in Children
Dysport should only be used in children for the treatment of cerebral palsy. For the treatment
of cerebral palsy spasticity in children, Dysport should only be used in children over 2 years
of age.
The safety and effectiveness of Dysport for the above approved adult indications have not
been demonstrated in children.

Use in the Elderly
A reduced dose may be appropriate in elderly patients where reduced muscle mass may exist.

Use in renal or hepatic impairment
No information is available on the use of Dysport in this population.

Carcinogenicity
Long term animal studies to evaluate the carcinogenic potential of Dysport have not been
performed.

Genotoxicity
No studies to assess the mutagenic potential of Dysport have been conducted.

Interaction with Other Medicines
Any drugs which interfere with neuromuscular transmission, such as muscle relaxants; or
drugs which interfere with the intraneuronal concentrations of Ca\(^{2+}\), have the potential to
interact with botulinum type A toxin. Aminoglycoside antibiotics cause flaccid paralysis by a
similar mechanism to that of botulinum neurotoxin. Therefore, in patients undergoing
treatment with Dysport, the additive action of aminoglycoside antibiotics may raise the total
neuromuscular blockade to the minimum required for an overt effect. Other drugs that may
react pharmacologically with botulinum type A toxin include penicillamine, procainamide,
spectinomycin, polymixins, tetracyclines and lincomycin. Such drugs should be used with
caution in patients treated with botulinum toxin.

Effects on ability to drive and use machines:
There is a potential risk of muscle weakness or visual disturbances which, if experienced,
may temporarily impair the ability to drive or operate machinery.

ADVERSE EFFECTS:-

The following section is presented in terms of, firstly, those adverse effects which have been
reported in association with the use of Dysport in all approved indications and secondly, any
additional adverse effects associated with each specific indication for which Dysport may be
used. Only those adverse effects which are considered possibly or probably related to
treatment with Dysport are included in this section and the frequency of reporting is indicated
as follows:
Very common >1/10: Common >1/100, <1/10: Uncommon >1/1000, <1/100: Rare >1/10 000, <
1/1000: Very rare <1/10 000.

General
In clinical trials in patients suffering from blepharospasm, hemifacial spasm, torticollis or
spasticity associated with cerebral palsy or stroke, approximately 30% of patients treated with
Dysport experienced an adverse event.

Nervous system disorders
Rare: Neuralgic amyotrophy / muscular atrophy

Skin and subcutaneous tissue disorders
Uncommon: Itching
Rare: Skin rashes including rashes at the injection site

**General disorders and administration site conditions**
Common: Generalised weakness, fatigue (exhaustion, lethargy, tiredness, and/or asthenia), ‘flu-like syndrome, pain / bruising / swelling / reddening at injection site

**Adult spasticity of the upper limb post-stroke**

In controlled studies the following adverse effects were recorded/observed:

**General disorders and administration site conditions**
Common: As expected for any injection procedure, injection site reactions (e.g. pain, erythema, swelling etc.) have been reported following administration of DYSPORT®.  
Uncommon: Asthenia, Fatigue, Influenza like illness

**Gastrointestinal disorders**
Common: Dysphagia

**Musculoskeletal and connective tissue disorders**
Common: Muscular weakness  
Rare: Severe pain in the affected upper limb

**Injury, poisoning and procedural complications**
Common: Accidental injury / falls

**Respiratory, thoracic and mediastinal disorders**
Rare: Exacerbation of night time cough

In the open-label studies the following undesirable effects were also observed:

**General disorders and administration site conditions:** Gait disturbance, Injection site bruising and haemorrhage  
**Musculoskeletal and connective tissue disorders:** Musculoskeletal pain, Pain in extremity  
**Nervous system disorders:** Hypertonia  
**Gastrointestinal disorders:** Dysphagia

**Spasmodic torticollis**

In 21 clinical trials involving approximately 4100 patients the following adverse effects were reported:

**Nervous system disorders**
Common: Headache, dizziness, facial paresis

**Eye disorders**
Common: Blurred vision, visual acuity reduced  
Uncommon: Diplopia

**Respiratory, thoracic and mediastinal disorders**
Common: Dysphonia, dyspnoea  
Rare: Aspiration, pharyngitis
Gastrointestinal disorders

Very common: Dysphagia, dry mouth

Musculoskeletal and connective tissue disorders

Very common: Muscle weakness
Common: Neck pain, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal stiffness
Uncommon: Muscle atrophy, jaw disorder

Dysphagia appeared to be dose related and occurred most frequently following injection into the sternomastoid muscle. A soft diet may be required until symptoms resolve.

In addition, during clinical trials, there have been reports of increased salivation in two patients, the causality of which was not assessed by the reporting investigator.

Dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older

In 14 clinical trials involving approximately 900 patients treated with Dysport, the following adverse effects were reported:

Gastrointestinal disorders

Common: Diarrhoea
Uncommon: Vomiting

Musculoskeletal and connective tissue disorders

Common: Leg muscle weakness

Renal and urinary disorders

Common: Urinary incontinence

General disorders and administration site conditions

Common: Abnormal gait
Uncommon: Somnolence

Injury, poisoning and procedural complications

Common: Accidental injury due to falling

Accidental injury due to falling and abnormal gait may have been due to the over-weakening of the target muscle and / or the local spread of Dysport to other muscles involved in ambulation and balance.

In a retrospective uncontrolled study, there were 3 reports of leg pain, for which the reporter did not provide a causality assessment. In these clinical studies, the incidence of convulsions in patients treated with Dysport was similar to that of the placebo groups, and reflects one of the most concomitant problems associated with cerebral palsy.

Blepharospasm and hemifacial spasm

In 13 clinical trials involving approximately 1400 patients treated with Dysport the following adverse effects were reported:
Nervous system disorders

Common: Facial muscle weakness
Uncommon: Facial paralysis

Eye disorders

Very common: Ptosis
Common: Diplopia, dry eyes, tearing
Rare: Ophthalmoplegia, photophobia, lagophthalmos

Skin and subcutaneous tissue disorders

Common: Eyelid oedema
Rare: Entropion

In addition there was 1 report of dysphagia, 19 reports of facial stiffness / numbness, 4 reports of conjunctivitis, 2 reports of facial swelling and 3 reports of local burning sensation from a clinical trial where the reporting investigator did not provide an assessment of causality of the reaction with treatment with Dysport.

Glabellar lines

In clinical studies, over 1500 patients with moderate to severe glabellar lines have been treated at the recommended dose of 50 Units in double-blind placebo-controlled (Y-97-52120-718 and Y-97-52120-719) and long-term open-label (Y-97-52120-720) studies.

In double-blind placebo-controlled single dose studies, 22.5% of patients treated at the recommended Dysport dose (50U) and 16.6% of patients treated with placebo, experienced an adverse effect that was related to treatment. In the long-term open-label dose Phase III study in which patients received multiple injection cycles, 26% of patients experienced at least one treatment related adverse effect after the first injection. The incidence of treatment related adverse effects decreased over repeat cycles.

The most frequently occurring related adverse effects are headache and injection site reactions. Most of the adverse effects reported were of mild to moderate severity.

Patients receiving the recommended dose of 50 units experienced the following adverse effects.

Nervous system disorders

Very common: Headache
Common: Facial paresis

Eye disorders

Common: Asthenopia, ptosis, eyelid oedema, lacrimation increase, dry eye, muscle twitching
Uncommon: Visual disturbances, vision blurred, diplopia, eye movement disorder

Skin and subcutaneous tissue disorders

Uncommon: Pruritis, skin rash
Rare: Urticaria

Immune System Disorders

Uncommon: Hypersensitivity

Musculoskeletal and connective tissue disorders
Common: Weakness of adjacent muscle to the area of injection. This may commonly lead to eyelid ptosis, asthenopia or uncommonly to paresis of facial muscles or visual disturbances.

**General disorders and administration site conditions**

Very common: Injection site reactions (including pain, bruising, pruritis, paraesthesia, erythema, rash). Note these events were also frequently seen in placebo group.

Injection site haemorrhage was also noted in an open label study.

Side effects may occur due to deep or misplaced injections of Dysport temporarily paralysing other nearby muscle groups.

**Post-Marketing reports**

The profile of adverse effects reported to the company during post-marketing use reflects the pharmacology of the product and those seen during clinical trials. During post-marketing surveillance studies, ptosis was rarely observed in patients treated for spasmodic torticollis. In addition in the same studies, nausea was reported as uncommon.

During a post-marketing surveillance study a number of reports of neck / shoulder pain (22), unspecified pain (10), heavy head / neck / shoulder (5), local pain (2), rigid neck (1), muscle soreness (1), ear pain (1), back pain (1), neck tension (1), arm pain (1), heavy arm (1), neuralgia (1) and muscle pain (1) were received which were assessed by the reporters as being related to treatment.

**Hypersensitivity:** There have been occasional reports of hypersensitivity.

**Adverse effects resulting from distribution of the effects of the toxin:** Adverse effects resulting from distribution of the effects of the toxin to sites remote from the site of injection have been very rarely reported (excessive muscle weakness, dysphagia, aspiration pneumonia that may be fatal).

**DOSAGE AND ADMINISTRATION:-**

THE UNITS OF DYSPORT ARE SPECIFIC TO THE PREPARATION AND ARE NOT INTERCHANGEABLE WITH OTHER PREPARATIONS OF BOTULINUM TYPE A TOXIN.

**Training:** Dysport should only be administered by appropriately trained physicians. The product distributor can facilitate training in administration of Dysport injections.

**Adult spasticity of the upper limb post-stroke**

The recommended dose range is 500–1000 units. The maximum dose administered must not exceed 1000 units.

The dose should be distributed amongst the following five muscles: flexor digitorum profundus (FDP), flexor digitorum superficialis (FDS), flexor carpi ulnaris (FCU), flexor carpi radialis (FCR) and biceps brachii (BB). The sites of injection can be chosen using electromyography as a guide or by palpation using anatomical landmarks. All muscles except the biceps brachii will be injected at one site, whilst the biceps will be injected at two sites. The recommended distribution of doses is given below:
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<tr>
<th></th>
<th>BB (units)</th>
<th>FDP (units)</th>
<th>FDS (units)</th>
<th>FCU (units)</th>
<th>FCR (units)</th>
<th>Total Dose (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysport</td>
<td>300-400</td>
<td>150</td>
<td>150-250</td>
<td>150</td>
<td>150</td>
<td>1,000</td>
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The lower starting dose of 500 units should be used if there is evidence to suggest that higher doses may result in excessive weakness of the target muscles, such as for patients whose target muscles are small, where the BB muscle is not to be injected or patients who are to be administered multi-level injections. Clinical improvement may be expected within two weeks after injection. Injections may be repeated approximately every 16 weeks, or as required to maintain response, but not more frequently than every 12 weeks.

**Spasmodic torticollis**

The doses recommended for the treatment of torticollis are applicable to adults of all ages providing they are of normal weight and have no evidence of reduced neck muscle mass. A lower dose may be appropriate if the patient is markedly underweight, or in the elderly and in women, where a reduced muscle mass may exist.

The recommended initial dose for the treatment of spasmodic torticollis is 250-500 units per patient given as a divided dose and administered into the two or three most active neck muscles.

For rotational torticollis distribute the optimal dose by administering 70% of the dose into the splenius capitis muscle, ipsilateral to the direction of the chin/head rotation and 30% of the dose into the sternomastoid muscle, contralateral to the rotation.

For laterocollis, distribute the optimal dose by administering 70% of the dose into the ipsilateral splenius capitis muscle and 30% of the dose into the ipsilateral sternomastoid muscle. In cases associated with shoulder elevation the ipsilateral trapezius or levator scapulae muscles may also require treatment, according to visible hypertrophy of the muscle or electromyographic (EMG) findings. Where injections of three muscles are required, distribute 60% of the optimal dose into the splenius capitis, 20% into the sternomastoid and 20% into the third muscle.

For retrocollis distribute the optimal dose by administering 50% of the dose into each of the splenius capitis muscles. Bilateral splenii injections may increase the risk of neck muscle weakness.

All other forms of torticollis are highly dependent on specialist knowledge and EMG to identify and treat the most active muscles. EMG should be used diagnostically for all complex forms of torticollis, for reassessment after unsuccessful injections in non complex cases, and for guiding injections into deep muscles or in overweight patients with poorly palpable neck muscles.

On subsequent administration, the doses may be adjusted according to the clinical response and side effects observed. Doses within the range of 250-1000 units are recommended, although the higher doses may be accompanied by an increase in side effects, particularly dysphagia. The maximum dose administered must not exceed 1000 units.

The relief of symptoms of torticollis may be expected within a week after the injection. Injections should be repeated approximately every 16 weeks or as required to maintain a response, but not more frequently than every 12 weeks.

**Dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older**

The initial recommended dose is 20 units/kg bodyweight given as a divided dose between both calf muscles. If only one calf is affected, a dose of 10 units/kg bodyweight should be used. Consideration should be given to lowering this starting dose if there is evidence to
suggest that this dose may result in excessive weakness of the target muscles, such as for patients whose target muscles are small or patients who require concomitant injections to other muscle groups. Following evaluation of response to the starting dose subsequent treatment may be titrated within the range 10 units/kg and 30 units/kg divided between both legs. The maximum dose administered must not exceed 30 units/kg or 1000 units/patient/session, whichever is lower.

Administration should primarily be targeted to the gastrocnemius, although injections of the soleus and injection of the tibialis posterior should also be considered.

The use of electromyography (EMG) is not routine clinical practice but may assist in identifying the most active muscles.

Clinical improvement may be expected within two weeks after injection. Injections may be repeated approximately every 16 weeks or as required to maintain response, but not more frequently than every 12 weeks.

**Blepharospasm and hemifacial spasm**

In a dose ranging clinical trial of the use of Dysport for the treatment of benign essential blepharospasm a dose of 40 units per eye was significantly effective. A dose of 80 units per eye resulted in a longer duration of effect. Thus, if a dose of 40 units per eye is chosen for the initial treatment, the patient may benefit from a dose of 80 units per eye for subsequent treatments if a longer duration of action is required. However the incidence of local adverse events, specifically ptosis, was dose related.

For an initial dose of 40 units per eye, injection of 10 units should be made medially and of 10 units should be made laterally into the junction between the preseptal and orbital parts of both the upper (3 and 4) and lower orbicularis oculi muscles (5 and 6) of each eye. Dependant on the muscles involved in the blepharospasm symptoms in the patient treated, additional injections in sites 1 and 2 may be necessary.

In order to reduce the risk of ptosis, injections near the levator palpebrae superioris should be avoided.

For injections into the upper lid the needle should be directed away from its centre to avoid the levator muscle. A diagram to aid placement of these injections is provided. The relief of symptoms may be expected to begin within two to four days with maximal effect within two weeks.

Injections should be repeated approximately every twelve weeks or as required to prevent recurrence of symptoms but not more frequently than every twelve weeks. On such subsequent administrations, if the response from the initial treatment is considered insufficient, the dose per eye may need to be increased to 60 units: 10 units medially and 20 units laterally, 80 units: 20 units medially and 20 units laterally or up to 120 units: 20 units medially and 40 units laterally above and below each eye in the manner previously described.

In cases of unilateral blepharospasm the injections should be confined to the affected eye. Patients with hemifacial spasm should be treated as for unilateral blepharospasm. The doses recommended are applicable to adults of all ages including the elderly.
In the treatment of blepharospasm and hemifacial spasm, the maximum dose must not exceed the total dose of 120 units per eye.

**Glabellar Lines**

Remove any make-up and disinfect the skin with a local antiseptic. Anatomical landmarks can be more readily identified if observed and palpated at maximum frown. Before injection, place the thumb or index finger firmly below the orbital rim in order to prevent extravasation below the orbital rim.

Intramuscular injection should be performed at right angles to the skin using a sterile 29-30 gauge needle. The needle should be pointed upward and medially during the injection.

The recommended dose is 50 units (0.25 mL) of Dysport to be divided equally among 5 injection sites. 10 units are to be administered intramuscularly into each of the 5 sites as follows:

- **Corrugator muscles**: A total of 4 injections (2 into each of the left and right corrugator muscles) at 5 mm intervals. The more medial of the two corrugator points on each side is localised on a vertical line, parallel to but 8 mm lateral to the medial vertical line and at a point on this vertical line 8 mm above the superior orbital margin. On the diagram below this is shown as site 2. The more lateral corrugator injections (site 3) should be placed at least 1 cm (i.e. 10 mm) above the bony supraorbital ridge (orbital rim) and 5 mm from the injection site 2.

- **Procerus muscle (site 1)**: One injection into the procerus muscle at the intersection of the medial vertical line and the horizontal line at the level of the naso-frontal angles.

In order to reduce the risk of ptosis, injection near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercili).

The treatment interval depends on the individual patient response following assessment. In clinical studies, some patients were still responding to treatment for up to 4 months after injection. Some patients were still responders at 5 months (see ‘Clinical Trials’ section). There should be a minimum interval of 12 weeks between treatments.

Children: Use of the product is not recommended for the temporary improvement of moderate to severe glabellar lines in patients under 18 years of age.

**Method of administration**
The exposed central portion of the rubber stopper should be cleaned with alcohol immediately prior to piercing the septum. A sterile 23 or 25 gauge needle should be used. The product should be reconstituted as described below and injected as described above for each specific indication.

**Spasticity of the upper limb post-stroke, spasmodic torticollis, paediatric cerebral palsy spasticity**

Dysport is administered by intramuscular injection for the indications listed above.
Dysport 500U is reconstituted with 1.0 mL of sodium chloride injection BP (0.9%) to yield a solution containing 500 units per mL of Dysport.
Dysport 300U is reconstituted with 0.6mL of sodium chloride injection B.P. (0.9%) to yield a solution with a concentration equivalent to 500 units per mL of Dysport.

**Blepharospasm, hemifacial spasm, glabellar lines**

When treating blepharospasm, hemifacial spasm and glabellar lines:
Dysport 500U is reconstituted with 2.5 mL of sodium chloride injection BP (0.9%) to yield a solution containing 200 units per mL of Dysport.
Dysport 300U is reconstituted with 1.5 mL of sodium chloride injection BP (0.9%) to yield a solution containing 200 units per mL of Dysport.
Dysport 125U is reconstituted with 0.63 mL of sodium chloride injection BP (0.9%) to yield a solution containing 200 units per mL of Dysport. The accurate measurement of 0.63mL can be achieved using 1mL insulin type syringes. These are graduated to 1 mL in 0.1 mL and 0.01 mL increments.

Dysport is administered by
- subcutaneous injection for the treatment of blepharospasm and hemifacial spasm
- intramuscular injection for the treatment of glabellar lines

### Reconstitution of Dysport 125U, 300U, 500U per vial (according to indication specific instructions described above)

<table>
<thead>
<tr>
<th>Dysport Presentation</th>
<th>Solvent added to vial (Sodium chloride 0.9% injection)</th>
<th>Resulting dose concentration (Dysport Units / 0.1mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 units/vial</td>
<td>1.0 mL</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>2.5 mL</td>
<td>20.0</td>
</tr>
<tr>
<td>300 units/vial</td>
<td>0.6 mL</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>1.5 mL</td>
<td>20.0</td>
</tr>
<tr>
<td>125 units/vial</td>
<td>0.63 mL</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Instructions for use / handling
Dysport contains no antimicrobial agent. The product should be administered within one hour of reconstitution to reduce microbiological hazard. If required it may be held between 2°C and 8°C for 24 hours after reconstitution. The product is for treatment of one patient only on one occasion. Discard any remaining contents.

Immediately after treatment of the patient, any residual Dysport which may be present in either vial or syringe should be inactivated with dilute hypochlorite solution (1% available chlorine). Thereafter, all items should be disposed of in accordance with standard hospital practice. Spillage of Dysport should be wiped up with an absorbent cloth soaked in dilute hypochlorite solution.

**OVERDOSAGE:-**
Excessive doses may produce distant and profound neuromuscular paralysis. Overdose could lead to an increased risk of the neurotoxin entering the bloodstream and may cause complications associated with the effects of oral botulinum poisoning (e.g. dysphagia and dysphonia). Respiratory support may be required where excessive doses cause paralysis of
respiratory muscles. There is no specific antidote; antitoxin should not be expected to be beneficial and general supportive care is advised. In the event of overdose the patient should be medically monitored for any signs and/or symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment should be instigated if necessary.

Symptoms of overdose may not present immediately following injection. Should accidental injection or oral ingestion occur the patient should be medically supervised for several weeks for any signs and/or symptoms of excessive muscle weakness or muscle paralysis. Contact the Poisons Information Centre on 131126 for advice on management of overdose.

**PRESENTATION AND STORAGE CONDITIONS:**
Dysport 125U / vial: Each vial contains 125 units of *Clostridium botulinum* type A toxin-haemagglutinin complex as a white lyophilised powder for reconstitution.
Dysport 300U / vial: Each vial contains 300 units of *Clostridium botulinum* type A toxin-haemagglutinin complex as a white lyophilised powder for reconstitution.
Dysport 500U / vial: Each vial contains 500 units of *Clostridium botulinum* type A toxin-haemagglutinin complex as a white lyophilised powder for reconstitution.

Boxes of 1 vial are available. Other excipients include albumin and lactose.

*Note: 125U formulation of Dysport is not yet marketed.*

**Storage**
Unopened vials must be maintained at temperatures between 2°C and 8°C.

Dysport must be stored in a refrigerator at the hospital where the injections are to be carried out and should not be given to the patient to store. Dysport should not be frozen.

**POISON SCHEDULES:-** S4

**SPONSOR:**
Ipsen Pty Ltd
Level 2, Building 4
Brandon Office Park
540 Springvale Road
Glen Waverley Victoria 3150

**AUSTR No:** 235282 (125U), 170651 (300U) and 74124 (500U)

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