1. PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

DYSPORT® 500 units, powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 U of *Clostridium botulinum* type A toxin-haemagglutinin complex.

Contains sugar (lactose monohydrate) 2,5 mg per vial.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection.

DYSPORT® is a white freeze-dried pellet with no foreign matter present.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DYSPORT® should be used when currently acceptable treatment modalities have failed. It should always be used in conjunction with physiotherapy/occupational therapy where appropriate and as part of a comprehensive treatment programme.

DYSPORT® is indicated for symptomatic treatment of focal spasticity of:

- Dynamic equinus foot deformity in ambulant paediatric cerebral palsy patients, two years of age or older
- Upper limbs in paediatric cerebral palsy patients, two years of age or older
- Upper limbs in adults.
- Lower limbs in adults affecting the ankle joint due to stroke or traumatic brain injury (TBI).

DYSPORT® is indicated in adults for symptomatic treatment of:

- Spasmodic torticollis
- Blepharospasm

- Hemifacial spasm
- Severe primary hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics

DYSPORT® is indicated for the temporary improvement in the appearance of moderate to severe:

- Glabellar lines (vertical lines between the eyebrows) seen at maximum frown and/or
- Lateral canthal lines (crow's feet) seen at maximum smile

in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient.

4.2 Posology and method of administration

The units of DYSPORT® are specific to the preparation and are not interchangeable with other preparations of botulinum type A toxin.

DYSPORT® should only be administered by appropriately trained medical practitioner. For the treatment of focal spasticity, DYSPORT® can also be administered by healthcare professionals having received appropriate training and qualification in accordance with national guidelines.

For instructions on reconstitution of the powder for solution for injection, handling and disposal of vials please refer to section 6.6.

Focal spasticity in paediatric cerebral palsy patients, two years of age or older

DYSPORT® maximum total doses per treatment session and minimum times before retreatment

Limb	**Maximum total dose of DYSPORT® to be administered per treatment session**	**Minimum time before retreatment should be considered**
Single lower limb Both lower limbs	15 units/kg or 1000 units* 30 units/kg or 1000 units*	No sooner than 12 weeks
Single upper limb	16 units/kg or 640 units*	No sooner than 16 weeks

Both upper limbs	21 units/kg or 840 units*	
Upper and lower limbs	30 units/kg or 1000 units*	No sooner than 12-16 weeks

*whichever is lower

Please see below for full posology and method of administration by treatment indication.

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

Posology

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins. For treatment initiation, consideration should be given to start with a lower dose.

The maximum total dose of DYSPORT® administered per treatment session must not exceed 15 units/kg for unilateral lower limb injections or 30 units/kg for bilateral injections. In addition, the total DYSPORT® dose per treatment session must not exceed 1000 units or 30 units/kg, whichever is lower. The total dose administered should be divided between the affected spastic muscles of the lower limb(s). When possible the dose should be distributed across more than 1 injection site in any single muscle.

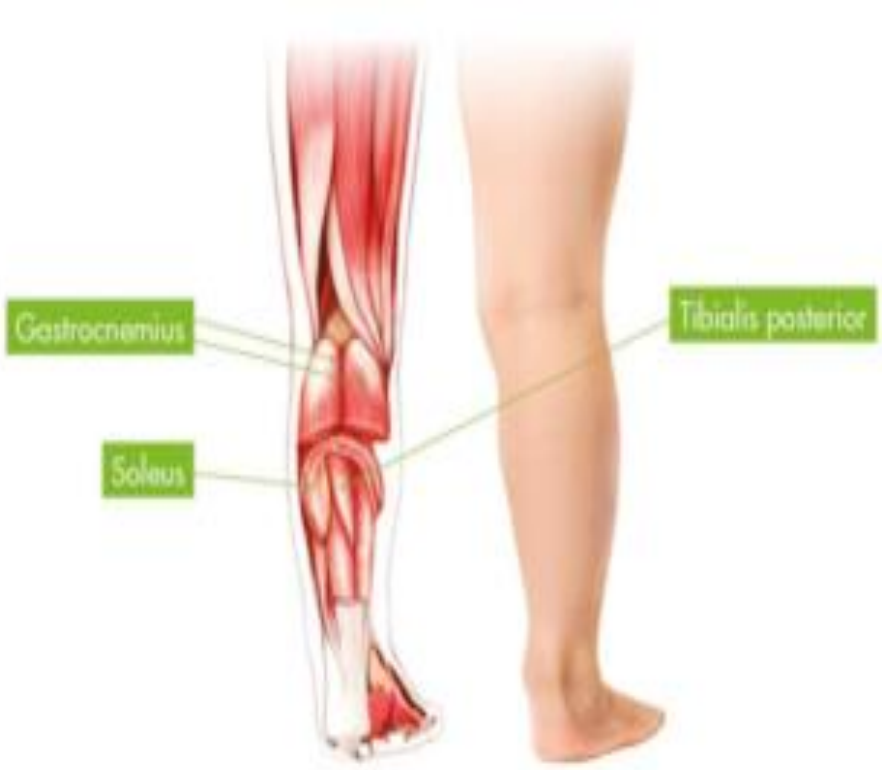
No more than 0,5 ml of DYSPORT® should be administered in any single injection site.

See below table for recommended dosing:

Muscle	**Recommended Dose Range per muscle per leg (U/kg Body weight)**	**Number of injection sites per muscle**
Distal		
Gastrocnemius	5 to 15 U/kg	Up to 4
Soleus	4 to 6 U/kg	Up to 2
Tibialis posterior	3 to 5 U/kg	Up to 2
Total dose	Up to 15 U/kg in a single lower limb or 30 U/kg if both lower limbs injected and not exceeding 1000 U*	

	Note: For concomitant treatment of upper and lower limbs the total dose should not exceed 30 U/kg or 1000 U*

* whichever is lower



Although actual location of the injection sites can be determined by palpation, the use of injection guiding technique, e.g. electromyography, electrical stimulation or ultrasound is recommended to target the injection sites.

Repeat DYSPORT® treatment should be administered when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection. A majority of patients in clinical studies were retreated between 16-22 weeks; however, some patients had a longer duration of response, i.e. 28 weeks. The degree_and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of DYSPORT® and muscles to be injected.

Clinical improvement may be expected within two weeks after injection.

Method of administration

When treating lower limb spasticity associated with cerebral palsy in children, DYSPORT® is reconstituted with sodium chloride injection BP (0,9 % w/v) (see also section 6.6) and is administered by intramuscular injection as detailed above.

Focal spasticity of upper limbs in paediatric cerebral palsy patients, two years of age or older

Posology

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins. For treatment initiation, consideration should be given to start with a lower dose.

The maximum dose of DYSPORT® administered per treatment session for unilateral upper limb injections must not exceed 16 U/kg or 640 U whichever is lower. When injecting bilaterally, the maximum DYSPORT® dose per treatment session must not exceed 21 U/kg or 840 U, whichever is lower.

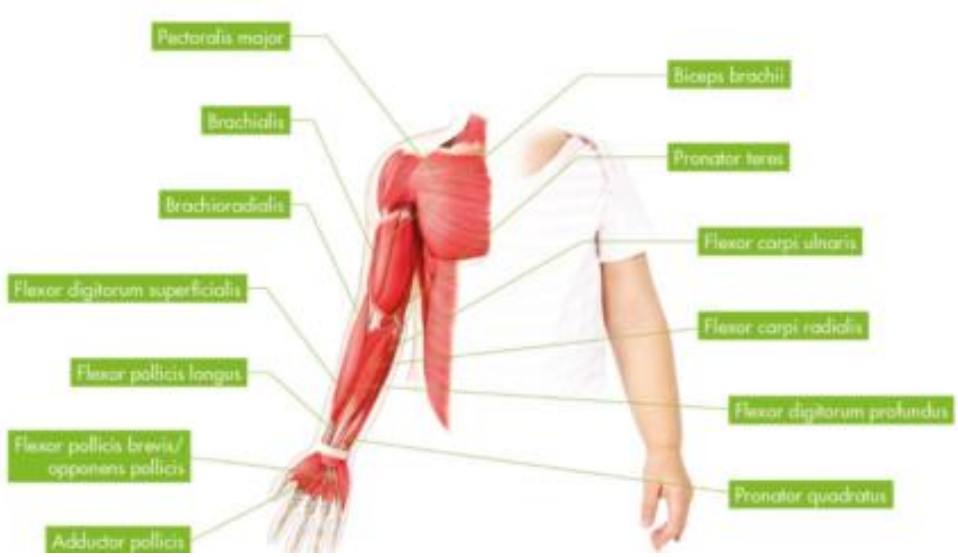
The total dose administered should be divided between the affected spastic muscles of the upper limb(s). No more than 0,5 ml of DYSPORT® should be administered in any single injection site. See table below for recommended dosing:

Botulinum Toxin Type A Dosing by Muscle for Paediatric Upper Limb Spasticity

Muscle	**Recommended Dose Range per muscle per upper limb (U/kg Body Weight)**	**Number of injection sites per muscle**
Brachialis	3 to 6 U/kg	Up to 2
Brachioradialis	1,5 to 3 U/kg	1
Biceps brachii	3 to 6 U/kg	Up to 2
Pronator teres	1 to 2 U/kg	1
Pronator quadratus	0,5 to 1 U/kg	1
Flexor carpi radialis	2 to 4 U/kg	Up to 2
Flexor carpi ulnaris	1,5 to 3 U/kg	1

Flexor digitorum profundus	1 to 2 U/kg	1
Flexor digitorum superficialis	1,5 to 3 U/kg	Up to 4
Flexor pollicis longus	1 to 2 U/kg	1
Flexor pollicis brevis/ opponens pollicis	0,5 to 1 U/kg	1
Adductor pollicis	0,5 to 1 U/kg	1
Pectoralis major	2,5 to 5 U/kg	Up to 2
Total dose	**Up to 16 U/kg or 640 U* in a single upper limb (and not exceeding 21 U/kg or 840 U* if both upper limbs injected)** **Note: For concomitant treatment of upper and lower limbs, the total dose should not exceed 30 U/kg or 1000 U***	

*whichever is lower



Although actual location of the injection sites can be determined by palpation the use of injection guiding technique, e.g. electromyography, electrical stimulation or ultrasound is recommended to target the injection sites.

Repeat DYSPORT® treatment should be administered when the effect of a previous

injection has diminished, but no sooner than 16 weeks after the previous injection. A majority of patients in the clinical study were retreated between 16-28 weeks; however some patients had a longer duration of response, i.e. 34 weeks or more. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of DYSPORT® and muscles to be injected.

Method of administration

When treating upper limb spasticity associated with cerebral palsy in children, DYSPORT® is reconstituted with sodium chloride injection (0,9 % w/v) (see section 6.6) and is administered by intramuscular injection as detailed above.

Focal spasticity of upper and lower limbs in paediatric cerebral palsy patients, two years of age or older

Posology

When treating combined upper and lower spasticity in children aged 2 years or older refer to the posology section for the individual indications above. The dose of DYSPORT® to be injected for concomitant treatment should not exceed a total dose per treatment session of 30 U/kg or 1000 U, whichever is lower.

Retreatment of the upper and lower limbs combined should be considered no sooner than a 12 to 16-week window after the previous treatment session. The optimal time to retreatment should be selected based on individuals progress and response to treatment.

Method of administration

When treating combined upper and lower spasticity associated with cerebral palsy in children refer to the method of administration section for the individual indications above.

Focal spasticity in adults

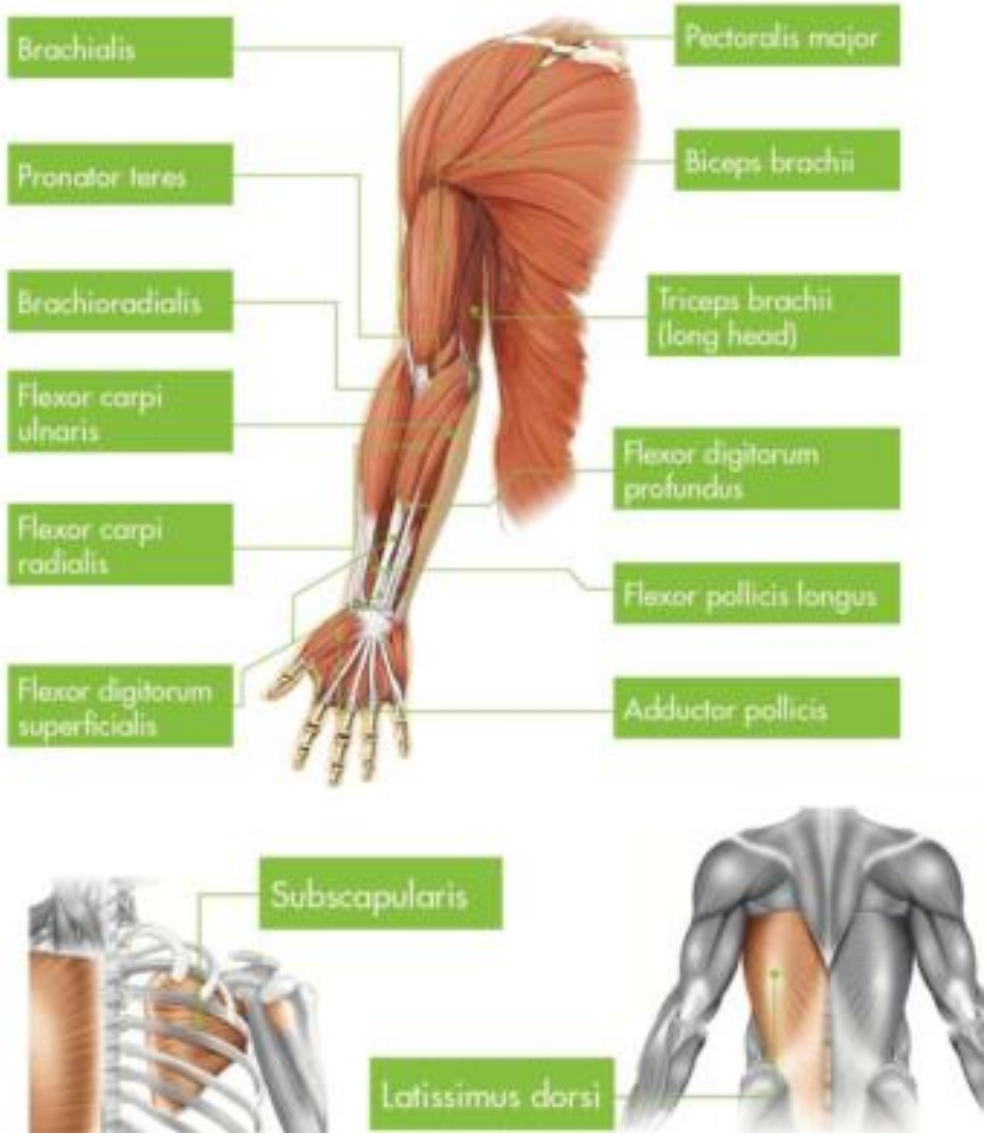
Upper limb:

Posology

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with DYSPORT®. In clinical trials, doses of 500 U and 1000 U were divided among selected muscles at a given treatment session as shown below.

No more than 1 ml should generally be administered at any single injection site. The total dose should not exceed 1000 units at a given treatment session.

Muscles Injected	**Recommended Dose DYSPORT® (U)**
Flexor carpi radialis (FCR)	100-200 U
Flexor carpi ulnaris (FCU)	100-200 U
Flexor digitorum profundus (FDP)	100-200 U
Flexor digitorum superficialis (FDS)	100-200 U
Flexor Pollicis Longus	100-200 U
Adductor Pollicis	25-50 U
Brachialis	200-400 U
Brachioradialis	100-200 U
Biceps Brachii (BB)	200-400 U
Pronator Teres	100-200 U
Triceps Brachii (long head)	150-300 U
Pectoralis Major	150-300 U
Subscapularis	150-300 U
Latissimus Dorsi	150-300 U



Although actual location of the injection sites can be determined by palpation, the use of injection guiding technique, e.g. electromyography, electrical stimulation or ultrasound is recommended to target the injection sites.

Clinical improvement may be expected one week after injection and may last up to 20 weeks. Injections may be repeated every 12 - 16 weeks or as required to maintain response, but not more frequently than every 12 weeks. The degree and pattern of muscle spasticity at the time of reinjection may necessitate alterations in the dose of DYSPORT® and muscles to be injected.

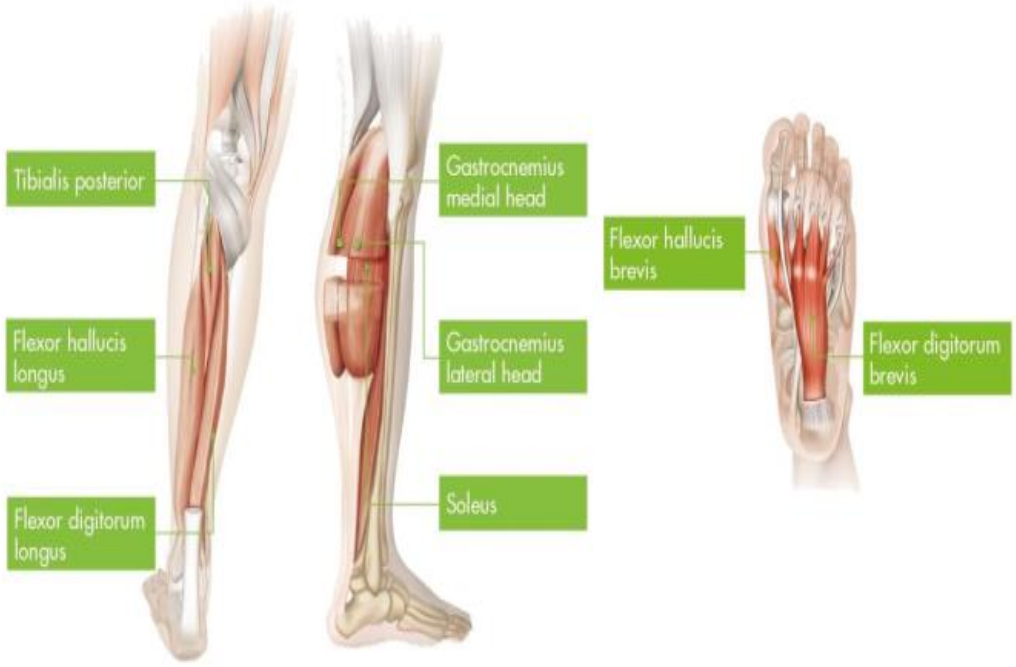
Lower limb spasticity affecting the ankle joints:

Posology

In clinical trials, doses of 1000 U and 1500 U were divided among selected muscles. The exact dosage in initial and sequential treatment sessions should be tailored to the individual based on the size and number of muscles involved, the severity of the spasticity, also taking into account the presence of local muscle weakness and the patient's response to previous treatment. However, the total dose should not exceed 1500 U.

No more than 1 ml should generally be administered at any single injection site.

Muscle	**Recommended Dose DYSPORT® (U)**	**Number of injection sites per muscle**
Primary target muscle		
Soleus muscle	300 – 550 U	2 - 4
Gastrocnemius:		
Medial head	100 – 450 U	1 – 3
Lateral head	100 – 450 U	1 – 3
Distal muscles		
Tibialis posterior	100 – 250 U	1 – 3
Flexor digitorum longus	50 – 200 U	1 – 2
Flexor digitorum brevis	50 – 200 U	1 – 2
Flexor hallucis longus	50 – 200 U	1 – 2
Flexor hallucis brevis	50 – 100 U	1 – 2



The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of DYSPORT® and muscles to be injected.

Although actual location of the injection sites can be determined by palpation, the use of injection guiding techniques, e.g. electromyography, electrical stimulation or ultrasound are recommended to help accurately target the injection sites.

Repeat DYSPORT® treatment should be administered every 12 to 16 weeks, or longer as necessary, based on return of clinical symptoms and no sooner than 12 weeks after the previous injection.

Upper and Lower limbs:

If treatment is required in the upper and lower limbs during the same treatment session, the dose of DYSPORT® to be injected in each limb should be tailored to the individual's need, according to the relevant posology and without exceeding a total dose of 1500 U.

Elderly patients (≥ 65 years): Clinical experience has not identified differences in response between the elderly and younger adult patients. In general, elderly patients should be observed to evaluate their tolerability of DYSPORT®, due to the greater frequency of concomitant disease and other medicine therapy.

Method of administration

When treating focal spasticity affecting the upper and lower limbs in adults, DYSPORT® is reconstituted with sodium chloride injection BP (0,9 % w/v) to yield a solution containing either 100 units per ml, 200 units per ml or 500 units per ml of DYSPORT® (see section 6.6).

DYSPORT® is administered by intramuscular injection into the muscles as described above.

Spasmodic torticollis

Posology

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

The initial recommended dose for the treatment of spasmodic torticollis is 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 500 units by administering 350 units into the *splenius capitis* muscle, ipsilateral to the direction of the chin/head rotation and 150 units into the *sternomastoid* muscle, contralateral to the rotation.
- For laterocollis, distribute the 500 units by administering 350 units into the ipsilateral *splenius capitis* muscle and 150 units into the ipsilateral *sternomastoid* muscle. In cases associated with shoulder elevation the ipsilateral *trapezoid* 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 the 500 units as follows, 300 units *splenius capitis*, 100 units *sternomastoid* and 100 units to the third muscle.
- For retrocollis distribute the 500 units by administering 250 units 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 may be repeated approximately every 16 weeks or as required to maintain a response, but not more frequently than every 12 weeks.

Children: The safety and effectiveness of DYSPORT® in the treatment of spasmodic torticollis in children have not been demonstrated.

Method of administration

When treating spasmodic torticollis, DYSPORT® 500 U vial is reconstituted with sodium chloride injection BP (0,9 % w/v) to yield a solution containing 500 units per ml of DYSPORT® (see section 6.6).

DYSPORT® is administered by intramuscular injection as described above.

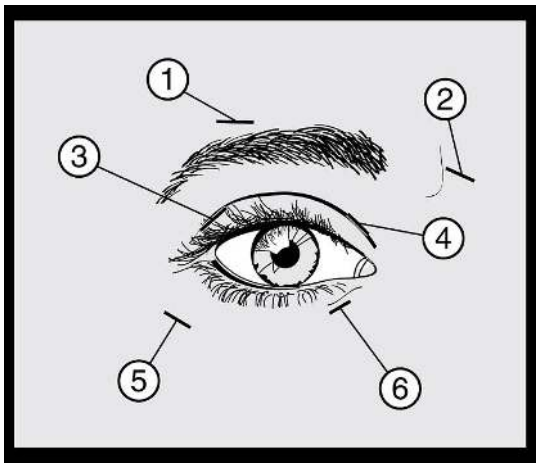
Blepharospasm and hemifacial spasm

Posology

In a dose ranging clinical trial on the use of DYSPORT® for the treatment of benign essential blepharospasm, a dose of 40 units per eye was significantly effective. Doses of 80 units and 120 units per eye resulted in a longer duration of effect. However, the incidence of local adverse events, specifically ptosis, was dose related. In the treatment of blepharospasm and hemifacial spasm, the maximum dose used must not exceed a total dose of 120 units per eye.

An injection of 10 units (0,05 ml) medially and 10 units (0,05 ml) laterally should be made 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. 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 above. 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 (0,05 ml) medially and 20 units (0,1 ml) laterally;
- 80 units: 20 units (0,1 ml) medially and 20 units (0,1 ml) laterally; or
- up to 120 units: 20 units (0,1 ml) medially and 40 units (0,2 ml) laterally,

above and below each eye in the manner previously described. Additional sites in the *frontalis* muscle above the brow (1 and 2) may also be injected if spasms here interfere with vision.

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.

Children: The safety and effectiveness of DYSPORT® in the treatment of blepharospasm and hemifacial spasm in children have not been demonstrated.

Method of administration

When treating blepharospasm and hemifacial spasm, DYSPORT® is reconstituted with sodium chloride injection BP (0,9 % w/v) to yield a solution containing 200 units per ml of DYSPORT® (see section 6.6).

DYSPORT® is administered by subcutaneous injection medially and laterally into the junction between the preseptal and orbital parts of both the upper and lower *orbicularis oculi* muscles of the eyes, as described above.

Moderate to severe glabellar lines and/or lateral canthal lines

Posology

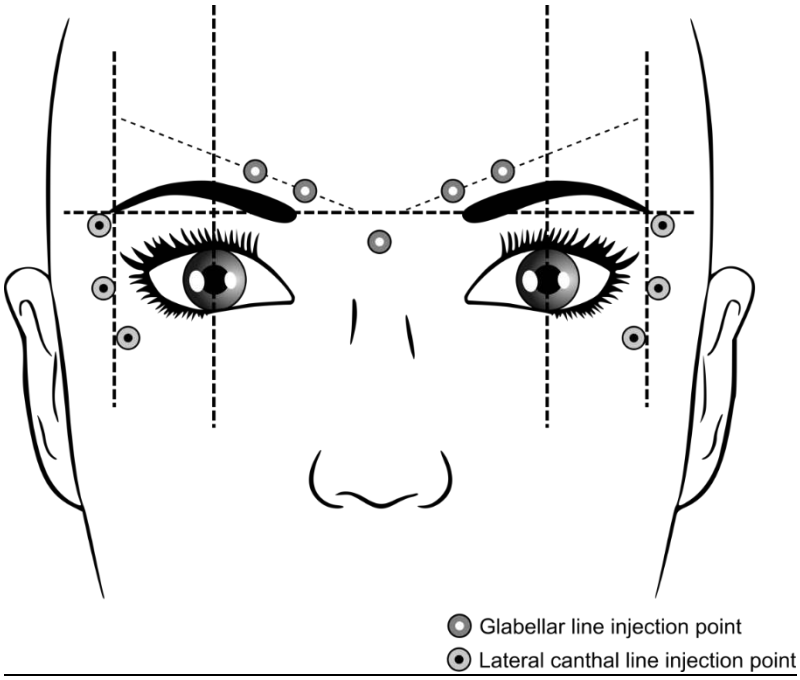
The treatment interval depends on the individual patient's response after assessment.

Treatment interval with DYSPORT® should not be more frequent than every three months.

Remove any make-up and disinfect the skin with a local antiseptic.

Intramuscular injections should be performed using a sterile 29 - 30 gauge needle.

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



Glabellar lines:

The recommended dose is 50 units (0,25 ml of reconstituted solution) of DYSPORT® to be divided into 5 injection sites, 10 units (0,05 ml of reconstituted solution) are to be administered intramuscularly, at right angles to the skin, into each of the 5 sites: 2 injections

into each *corrugator* muscle and one into the *procerus* muscle near the nasofrontal angle as shown above.

The anatomical landmarks can be more readily identified if observed and palpated at maximal frown. Before injection, place the thumb or index finger firmly below the orbital rim in order to prevent extravasation below the orbital rim.

The needle should be pointed upward and medially during the injection. In order to reduce the risk of ptosis, avoid injections near the *levator palpebrae superioris* muscle, particularly in patients with larger brow-depressor complexes (*depressor supercilii*). Injections in the *corrugator* muscle must be made into the central part of that muscle, at least 1 cm above the orbital rim.

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

Lateral canthal lines:

The recommended dose per side is 30 units (60 units for both sides, 0.30 ml of reconstituted solution) of DYSPORT®, to be divided into 3 injection sites; 10 units (0,05 ml of reconstituted solution) are to be administered intramuscularly into each injection point. Injection should be lateral (20 - 30° angle) to the skin and very superficial. All injection points should be at the external part of the *orbicularis oculi* muscle and sufficiently far from the orbital rim (approximately 1 - 2 cm) as shown above.

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

<u>General Information</u>

In the event of treatment failure or diminished effect following repeat injections, alternative treatment methods should be employed. In case of treatment failure after the first treatment session, the following approaches may be considered:

- Analysis of the causes of failure, e.g. incorrect muscles injected, inappropriate injection technique, and formation of toxin-neutralising antibodies
- Re-evaluation of the relevance of treatment with DYSPORT®.

The efficacy and safety, of repeat injections of DYSPORT®, has been evaluated in glabellar lines up to 24 months and up to 8 repeat treatment cycles and for lateral canthal lines up to 12 months and up to 5 repeat treatment cycles.

Children: The safety and effectiveness of DYSPORT®, in treating moderate to severe glabellar lines and lateral canthal lines, in individuals under 18 years of age have not been demonstrated

Method of administration

For moderate to severe glabellar lines or lateral canthal lines, DYSPORT® is reconstituted with sodium chloride injection BP (0,9 % w/v) to yield a solution containing 200 units per ml of DYSPORT® (see section 6.6).

Axillary hyperhidrosis

Posology

The recommended initial dosage is 100 units per axilla. If the desired effect is not attained, up to 200 units per axilla can be administered for subsequent injections. The maximum dose administered should not exceed 200 units per axilla.

The area to be injected should be determined beforehand using the iodine-starch test. Both axillae should be cleaned and disinfected. Intradermal injections at ten sites, each site receiving 10 units, i.e., to deliver 100 units per axilla, are then administered.

The maximum effect should be seen by week two after injection. In many cases, the recommended dose will provide adequate suppression of sweat secretion for approximately 48 weeks. The time point for further applications should be determined on an individual basis according to clinical need. Injections should not be repeated more frequently than every 12 weeks. There is some evidence for a cumulative effect of repeated doses so the time of each treatment for a given patient should be assessed individually.

Children: The safety and effectiveness of DYSPORT® in the treatment of axillary hyperhidrosis in children has not been demonstrated.

Method of administration

When treating axillary hyperhidrosis, DYSPORT® is reconstituted with sodium chloride solution BP (0,9 % w/v) to yield a solution containing 200 units per ml of DYSPORT® (see section 6.6).

DYSPORT® is administered by intradermal injection as described above.

4.3 Contraindications

DYSPORT® is contraindicated in:

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- presence of infection or inflammation at the proposed injection site(s),
- pregnancy and lactation.

4.4 Special warnings and precautions for use

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8) which, in some cases, was associated with dysphagia, pneumonia and/or significant debility resulting, very rarely, in death. Patients treated with therapeutic doses may present with excessive muscle weakness. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective possible dose and by not exceeding the maximum recommended dose.

DYSPORT® should only be used with caution and under close medical supervision in patients with subclinical or clinical evidence of marked defective neuromuscular transmission (e.g. myasthenia gravis). Such patients may have an increased sensitivity to medicines such as DYSPORT®, which may result in excessive muscle weakness with therapeutic doses. Patients with underlying neurological disorders are at increased risk of this side effect.

Caution should be exercised when treating adult patients especially the elderly, with focal spasticity affecting the lower limbs, who may be at increased risk of fall. In placebo-controlled clinical studies, where patients were treated for lower limb spasticity, 6,3 % and 3,7 % of patients experienced a fall in the DYSPORT® and placebo groups, respectively.

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

Cases of death, occasionally in a context of dysphagia, pneumopathy (including but not limited to dyspnoea, respiratory failure, respiratory arrest) and/or in patients with significant asthenia have been reported after treatment with botulinum toxin A or B. Patients with disorders resulting in defective neuromuscular 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.

DYSPORT® should be administered with caution to patients with pre-existing swallowing or breathing problems, as these can worsen following the distribution of the effect 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.

The recommended posology and frequency of administration for DYSPORT® must not be exceeded (see section 4.2).

Patients and their caregivers must be warned of the necessity to seek immediate medical treatment in case of swallowing, speech or respiratory problems.

DYSPORT® should not be used to treat spasticity in patients who have developed a fixed contracture.

DYSPORT® should only be used where strictly necessary in patients with prolonged bleeding times, infection or inflammation at the proposed site(s) of injection.

Caution should be taken when DYSPORT® is used where the targeted muscle shows excessive weakness or atrophy.

DYSPORT® should only be used to treat a single patient, during a single session.

Specific precautions must be taken during the preparation and administration of the product (see section 4.2) and for the inactivation and disposal of any unused reconstituted solution (see section 6.6).

Antibody formation to botulinum toxin has been noted rarely in patients receiving DYSPORT®. Clinically, neutralising antibodies might be suspected by a substantial

deterioration in response to therapy and/or the need for consistent use of increased doses.

This product contains a small amount of human albumin. The risk of transmission of viral infection cannot be excluded with absolute certainty.

When treating glabellar lines, it is essential to study the patient's facial anatomy prior to administration. Facial asymmetry, ptosis, excessive dermatochalasis, scarring and any alterations to this anatomy, as a result of previous surgical interventions should be taken into consideration.

Careful consideration should be given before the injection of patients who have experienced a previous allergic reaction to a product containing botulinum toxin type A. The risk of a further allergic reaction must be considered in relation to the benefit of treatment.

Should an anaphylactic reaction occur, the necessary precautions, e.g. epinephrine, must be available.

Patients should be warned about possible disturbances of vision following injection of DYSPORT®.

Contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not receive this medicine.

Paediatric use

For the treatment of spasticity associated with cerebral palsy in children, DYSPORT® should only be used in children of 2 years of age or over. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general, the dose used in these cases was in excess of that recommended (see section 4.8).

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off-label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with

poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

4.5 Interaction with other medicines and other forms of interaction

The effect of botulinum toxin may be enhanced by medicines interfering either directly or indirectly with neuromuscular function (e.g. aminoglycosides, curare-like non-depolarising blockers, muscle relaxants) and such medicines should be used with caution in patients treated with botulinum toxin due to the potential for undesirable effects.

4.6 Fertility, pregnancy and lactation

DYSPORT® is contraindicated in pregnancy and lactation.

Pregnancy:

There are limited data from the use of *Clostridium botulinum* type A toxin-haemagglutinin complex in pregnant women. Studies in animals have shown reproductive toxicity at high doses causing maternal toxicity (see section 5.3).

Breastfeeding:

It is not known whether *Clostridium botulinum* type A toxin-haemagglutinin complex is excreted in human milk. The excretion of *Clostridium botulinum* type A toxin-haemagglutinin complex in milk has not been studied in animals. The use of *Clostridium botulinum* type A toxin-haemagglutinin complex during lactation cannot be recommended.

Fertility:

Studies in male and female rats have shown effects on fertility (see section 5.3).

4.7 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.

4.8 Undesirable effects

General

Side effects related to spread of toxin distant from the site of administration have been reported, such as dry mouth, exaggerated muscle weakness, dysphagia, aspiration/aspiration pneumonia, with fatal outcome in some very rare cases (see section 4.4). Hypersensitivity reactions have also been reported post-marketing.

The frequency of adverse reactions reported in placebo-controlled trials after a single administration is defined as follows: Very common >1/10; Common >1/100, <1/10; Uncommon >1/1000, <1/100; Rare >1/10 000, <1/1000.

The following adverse reactions were seen in patients treated across a variety of indications including blepharospasm, hemifacial spasm, torticollis, spasticity associated with either cerebral palsy or stroke/TBI and axillary hyperhidrosis:

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Nervous system disorders	Rare	Neuralgic amyotrophy
Skin and subcutaneous tissue disorder	Uncommon	Pruritus
	Rare	Rash
General disorders and administration site conditions	Common	Asthenia, fatigue, flu-like illness and injection site reactions (e.g. pain, bruising, pruritus, oedema)

Frequency of specific adverse reactions by indication

In addition, the following adverse reactions specific to individual indications were reported:

Dynamic equinus foot deformity due to focal spasticity in ambulant paediatric cerebral palsy patients, 2 years of age or older

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Musculoskeletal and connective tissue disorders	Common	Myalgia, muscular weakness
Renal and urinary disorders	Common	Urinary incontinence
General disorders and administration site conditions	Common	Influenza-like illness, injection site reaction (e.g. pain, erythema, bruising etc.), gait disturbance, fatigue
	Uncommon	Asthenia
Injury, poisoning and procedural complications	Common	Fall

Focal spasticity of upper limbs in paediatric cerebral palsy patients, two years of age or older

System Organ Class	Frequency	Adverse Drug Reaction
Musculoskeletal and connective tissue disorders	Common	Muscular weakness, pain in extremity
	Uncommon	Myalgia
General disorders and administration site conditions	Common	Influenza-like illness, asthenia, fatigue, injection site bruising
	Uncommon	Injection site eczema, injection site pain, injection site rash, injection site swelling
Skin and subcutaneous tissue disorders	Common	Rash

Focal spasticity of upper and lower limbs in paediatric cerebral palsy patients, two years of age or older

When treating upper and lower limbs concomitantly with DYSPORT® at a total dose of up to 30 U/kg or 1000 U whichever is lower, there are no safety findings in addition to those expected from treating either upper limb or lower limb muscles alone.

Focal spasticity affecting the upper limbs in adults

System Organ Class	Frequency	Adverse Drug Reaction
Gastrointestinal disorders	Uncommon	Dysphagia*
Musculoskeletal and connective tissue disorders	Common	Muscular weakness, musculoskeletal pain, pain in the extremities

*The frequency for Dysphagia was derived from pooled data from open-label studies.

Dysphagia was not observed in the double-blind studies in the Adult Upper Limb (AUL) indication

Focal spasticity affecting the lower limbs in adults

System Organ Class	Frequency	Adverse Drug Reaction
Gastrointestinal disorders	Common	Dysphagia

Musculoskeletal and connective tissue disorders	Common	Muscular weakness, myalgia
General disorders and administration site conditions	Common	Asthenia, fatigue, influenza-like illness, injection site reactions (pain, bruising, rash, pruritus)
Injury, poisoning and procedural complications	Common	Fall

Spasmodic torticollis

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Nervous system disorders	Common	Headache, dizziness, facial paresis
Eye disorders	Common	Blurred vision, reduced visual acuity
	Uncommon	Diplopia, ptosis
Respiratory, thoracic and mediastinal disorders	Common	Dysphonia, dyspnoea
	Rare	Aspiration
Gastrointestinal disorders	Very common	Dysphagia, dry mouth
	Uncommon	Nausea
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. These side effects may be expected to resolve within two to four weeks.

Blepharospasm and hemifacial spasm

System Organ Class	**Frequency**	**Adverse Drug Reaction**

Nervous system disorders	Common	Facial paresis
	Uncommon	VIIth nerve paralysis
Eye disorders	Very common	Ptosis
	Common	Diplopia, dry eye, lacrimation increased
	Rare	Ophthalmoplegia
Skin and subcutaneous tissue disorders	Common	Eyelid oedema
	Rare	Entropion

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

Moderate to severe glabellar lines

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Nervous system disorders	Very common	Headache
	Common	Temporary facial paresis (due to temporary paresis of facial muscles proximal to injection sites, predominantly describes brow paresis)
	Uncommon	Dizziness
Eye disorders	Common	Asthenopia, eyelid ptosis, eyelid oedema, lacrimation increased, dry eye, muscle twitching (twitching of muscles around the eyes)
	Uncommon	Visual disturbances, vision blurred, diplopia
	Rare	Eye movement disorder
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, rash
	Rare	Urticaria

General disorders and administration site conditions	Very common	Injection site reactions (e.g. erythema, oedema, irritation, rash, pruritus, paraesthesia, pain, discomfort, stinging and haematoma)
Immune system disorders	Uncommon	Hypersensitivity

Moderate to severe lateral canthal lines

System Organ Class	Frequency	Adverse Drug Reaction
Nervous system disorders	Very common	Headache, temporary facial paresis (temporary paresis of facial muscles proximal to injection sites)
Eye disorders	Common	Eyelid oedema, eyelid ptosis
	Uncommon	Dry eye
General disorders and administration site conditions	Common	Injection site reactions (e.g. haematoma, pruritus and oedema)

Axillary hyperhidrosis

System Organ Class	Frequency	Adverse Drug Reaction
Skin and subcutaneous tissue disorders	Common	Compensatory sweating

Post-marketing experience

System Organ Class	Frequency	Adverse Drug Reaction
Immune system disorders	Not Known	Hypersensitivity
Nervous system disorders	Not Known	Hypoaesthesia

Musculoskeletal and connective tissue disorders	Not Known	Muscle atrophy

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care provders are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Alternately you can contact Acino Pharma (Pty) Ltd:

E-mail: drugsafety_ZA@acino.swiss

4.9 Overdose

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.

General supportive care is advised. In the event of overdose, the patient should be medically monitored for 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 signs and/or symptoms of excessive muscle weakness or muscle paralysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.30.4. Biologicals. Other

Pharmacotherapeutic group: Other muscle relaxants, peripherally acting agents.

ATC code: M03AX01

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 the toxin involves an initial binding step whereby the toxin is attached to the presynaptic nerve membrane. Secondly, there is an internalisation step in which the 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 to 8 weeks.

5.2 Pharmacokinetic properties

Pharmacokinetic studies with botulinum toxin pose problems in animals because of the high potency, the minute doses involved, the large molecular weight of the compound and the difficulty of labelling toxin to produce sufficiently high specific activity. Studies using I^{125} labelled toxin have shown that the receptor binding is specific and saturable, and the high density of toxin receptors is a contributory factor to the high potency.

Dose and time responses showed that at low doses there was a delay in onset of effect of 2 to 3 days with peak effect seen 5 to 6 days after injection. The duration of action, measured by changes of ocular alignment and muscle paralysis, varied between 2 weeks and 8 months and is attributed to the process of binding, internalisation and changes at the neuromuscular junction.

5.3 Preclinical safety data

In a chronic toxicity study performed in rats, up to 12 units/animal, there was no indication of systemic toxicity. Reproductive toxicity studies in pregnant rats and rabbits given

Clostridium botulinum type A toxin-haemagglutinin complex by daily intramuscular injection, at doses of 6,6 units/kg (79 units/kg total cumulative dose) and 3,0 units/kg (42 units/kg total cumulative dose) in rats and rabbits respectively, did not result in embryo/foetal toxicity. Implantation losses at maternally toxic doses were observed at higher doses in both species. *Clostridium botulinum* type A toxin-haemagglutinin complex demonstrated no teratogenic activity in either rats or rabbits and no effects were observed in the pre- and post-natal study on the F1 generation in rats. Fertility of male and female rats was decreased due to reduced mating, secondary to muscle paralysis, at doses of 29,4 units/kg weekly in males and increased implantation loss at 20 units/kg weekly in females (see section 4.6).

In a pivotal single dose study, juveniles showed a slight delay in sexual maturation (not observed in the repeat dose study), an effect associated with decreased body weight, but subsequent mating performance and fertility were unaffected. In a pivotal repeated dose juvenile study, rats treated weekly from the age of weaning on Postnatal Day 21 up to 13 weeks of age comparable to children of 2 years old, to young adulthood (11 administrations over 10 weeks, up to total dose of approximately 33 units/kg) do not show adverse effects on postnatal growth (including skeletal evaluation), reproductive, neurological and neurobehavioral development.

The effects in reproduction, juvenile and chronic toxicity non-clinical studies were limited to changes in injected muscles related to the mechanism of action of *Clostridium botulinum* type A toxin-haemagglutinin complex.

There was no ocular irritation following administration of *Clostridium botulinum* type A toxinhaemagglutinin complex into the eyes of rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin

Lactose

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

Unopened vial:

2 years

Reconstituted solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Unopened vial:

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Reconstituted solution

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

DYSPORT® is filled into a 3 ml Type I clear neutral glass vial sealed with a halobutyl freeze-drying closure and self-coloured aluminium seal with flip-top.

Pack sizes of 1 or 2 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When preparing and handling DYSPORT®, the use of gloves is recommended. If DYSPORT® dry powder or reconstituted solution should come into contact with the skin or mucous membranes, they should be washed thoroughly with water.

Instruction for reconstitution

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. Each vial is for single use only.

Reconstitution instructions are specific for the 500 unit vial. These volumes yield concentrations specific for the use for each indication.

Resulting Dose Unit per ml	**Diluent* per 500 Unit Vial**
500 Units	1 ml
200 Units	2,5 ml
100 Units	5 ml

* Preservative-free 0,9 % Sodium Chloride Injection

For paediatric cerebral palsy spasticity, which is dosed using unit per body weight, further dilution may be required to achieve the final volume for injection

Appearance of product after reconstitution

A clear colourless solution, free from particulate matter.

Disposal

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).

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

Any unused product or waste material should be disposed of in accordance with local requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd.

106 16th Road

Midrand

8. REGISTRATION NUMBER(S)

37/30.4/0683

9. DATE OF FIRST AUTHORISATION

11 February 2005.

10. DATE OF REVISION OF THE TEXT

28 June 2024