**4.2 POSOLOGY AND METHOD OF ADMINISTRATION**

*Information included in section 4.2 is only relevant if the indication is approved.*

The units are specific to the preparations and are not interchangeable with other preparations of botulinum toxin.

Botulinum Toxin Type A-Hemagglutinin Complex should only be administered by appropriately trained physicians.

*Adult spasticity of the leg post-stroke:*

**Posology** The maximum dose is 1500 units, distributed between the gastrocnemius and soleus muscles although injections of the tibialis posterior should also be considered.

The use of electromyography (EMG) is not routine clinical practice but it may assist in identifying the most active muscles. The starting dose should be lowered 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 for patients who require concomitant injections into other muscle groups. 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 the product in the treatment of post-stroke leg spasticity in children have not been demonstrated.

**Method of administration** When treating post-stroke leg spasticity in adults, Botulinum Toxin Type A-Hemagglutinin Complex® is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing 500 units per ml of Botulinum Toxin Type A-Hemagglutinin Complex®. Botulinum Toxin Type A-Hemagglutinin Complex® is administered by intramuscular injection into the recommended muscles as detailed above.

*Adult spasticity of the arm post-stroke:*

**Posology** The recommended dose is 1000 units, 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).

All muscles (except the biceps brachii) will be injected at one site, whilst the biceps brachii will be injected at two sites. The recommended distribution of the total dose (in units) by muscle is given below.

The sites of injection may be guided by standard locations used for electromyography (EMG), although actual location of the injection sites should be determined by palpation. The starting
dose should be lowered 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, where the BB muscle is not to be injected or for patients who require concomitant injections into other muscle groups. 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 the product in the treatment of post-stroke arm spasticity in children have not been demonstrated.

Method of administration When treating post-stroke arm spasticity in adults, Botulinum Toxin Type A-Hemagglutinin Complex® is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing 500 units per ml of Botulinum Toxin Type A-Hemagglutinin Complex®. Botulinum Toxin Type A-Hemagglutinin Complex® is administered by intramuscular injection into the five muscles detailed above.

Local symptomatic treatment of spasticity affecting the upper and/or lower limbs in adults:

Posology When treating either upper or lower limb spasticity the posology and administration instructions are as described for the individual indications

When treating both the upper and the lower limbs during the same treatment session, the total dose injected should not exceed 1500 units

In the adult spasticity of the leg: The maximum dose is 1500 units, distributed between the gastrocnemius and soleus muscles although injections of the tibialis posterior or other lower limb muscles should also be considered if needed.

In the adult spasticity of the arm: The recommended dose is 1000 units, 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). 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 dose (in units) is given below.

In the treatment of spasticity of both the lower and upper limbs, working to a maximum dosage of 1500 units, the recommended distribution of the dose per muscle is shown in the following table: The injection site may be determined either by electromyographic guidance.
particularly for deep muscles) or after selection by muscle stimulation. In view of the technical difficulties involved, the injection into the posterior tibial muscle requires appropriate training and special competence on the part of the physician administering the injection.

The starting dose should be lowered 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, where the BB muscle is not to be injected or for patients who require concomitant injections into other muscle groups.

Injections may be repeated as required to maintain a clinical response, but not more frequently than every 12 weeks.

Children: The safety and effectiveness of the product in the treatment of spasticity affecting both the upper and lower limbs in children have not been demonstrated.

Method of administration. When treating combined upper and lower spasticity in adults, Botulinum Toxin Type A-Hemagglutinin Complex® is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing 500 units per ml and is administered by intramuscular injection as detailed above.

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

Note: The maximum 1000 units are approved in 22 EU countries and maximum 700 units are approved in 3 EU countries.

Posology The initial recommended dose is 20 units/kg of body weight given as a divided dose between both calf muscles. If only one calf is affected, a dose of 10 units/kg of body weight should be used. The maximum dose administered must not exceed 30 units/kg or 1000 units, whichever is lower.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Dose per muscle (unit): No. of injection sites per muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps brachii</td>
<td>300-400: 2 sites</td>
</tr>
<tr>
<td>Flexor digitorum profundus</td>
<td>150: 1 site</td>
</tr>
<tr>
<td>Flexor digitorum superficialis</td>
<td>150-250: 1 site</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>150: 1 site</td>
</tr>
<tr>
<td>Flexor carpi</td>
<td>150: 1 site</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>250-750: 1 or 2 sites</td>
</tr>
<tr>
<td>Soleus</td>
<td>250-750: 1 or 2 sites</td>
</tr>
<tr>
<td>Tibialis posterior</td>
<td>200-350: 1 or 2 sites</td>
</tr>
<tr>
<td>Flexor digitorum longus</td>
<td>150-300: 1 or 2 sites</td>
</tr>
<tr>
<td>Adductor</td>
<td>500-1500: 1 or 2 sites</td>
</tr>
</tbody>
</table>

1 The starting dose should to be lower, in order to avoid causing excessive weakness in the affected muscles, e.g. in patients in whom the muscles to be treated are under-developed or in patients who need a simultaneous injection into another muscle group. 2 The number of sites depends on the volume of the muscle that is being injected.
The use of electromyography (EMG) may assist in identifying the most active muscles. Injections may be repeated approximately every 16 weeks or as required to maintain response, but not more frequently than every 12 weeks. 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 for patients who require concomitant injections into other muscle groups.

Following evaluation of response to the starting dose, subsequent treatment may be titrated within the range of 10 units/kg and 30 units/kg divided between both legs. Administration should primarily be targeted to the *gastrocnemius*, although injection of the *soleus* and the *tibialis posterior* should also be considered.

**Method of administration** When treating paediatric cerebral palsy spasticity, *Botulinum Toxin Type A-Hemagglutinin Complex*® is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing 500 units per ml of *Botulinum Toxin Type A-Hemagglutinin Complex*®. *Botulinum Toxin Type A-Hemagglutinin Complex*® is administered by intramuscular injection into the calf muscles as described above.

**Spasmodic torticollis**

**Posology** The doses recommended for the treatment of torticollis are applicable to adults of all ages provided 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, where a reduced muscle mass may exist. The recommended initial dose for the treatment of spasmodic torticollis is 500 units given as a divided dose and administered into the two or three most active neck muscles.

On subsequent administration, doses may be adjusted according to both the clinical response and the 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. Injections may be repeated approximately every 16 weeks or as required to maintain a response, but not more frequently than every 12 weeks.

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 injection of three muscles is required,
distribute the 500 units as follows; 300 units into the splenius capitis, 100 units into the sternomastoid and 100 units into 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 following unsuccessful injections in non-complex cases, and for guiding injections into deep muscles or in overweight patients with poorly palpable neck muscles.

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

Method of administration When treating spasmodic torticollis, Botulinum Toxin Type A-Hemagglutinin Complex ® is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing 500 units per ml of Botulinum Toxin Type A-Hemagglutinin Complex . Botulinum Toxin Type A-Hemagglutinin Complex ® is administered by intramuscular injection as detailed above.

**Blepharospasm and hemifacial spasm**

Posology In a dose ranging clinical trial of the use of Botulinum Toxin Type A-Hemagglutinin Complex for the treatment of benign essential blepharospasm (BEB) a dose of 40 units per eye was significantly effective. A dose of 80 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. A diagram to aid placement of these injections is provided above. Injections should be repeated approximately every twelve weeks or as required to prevent the recurrence of symptoms, but not more frequently than every twelve weeks.
On such subsequent administrations, if the response following the initial treatment is considered insufficient, the dose per eye may need to be increased as follows: 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.

For cases of unilateral blepharospasm, 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 the product in the treatment of blepharospasm and hemifacial spasm in children have not been demonstrated.

**Method of administration** When treating blepharospasm and hemifacial spasm Botulinum Toxin Type A-Hemagglutinin Complex® is reconstituted with sodium chloride injection B.P (0.9% w/v) to yield a solution containing 200 units per ml of Botulinum Toxin Type A-Hemagglutinin Complex®. Botulinum Toxin Type A-Hemagglutinin Complex® 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.

**Axillary hyperhidrosis**

**Posology** The initial recommended dose is 100 units per axilla. If the desired effect is not attained with this dose, up to 200 units per axilla may be administered for subsequent injections. The maximum dose administered must 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 thoroughly and disinfected. Intradermal injections at ten sites, with each site receiving 10 units (i.e. 100 units per axilla), are then administered. The time point for further applications should be determined on an individual basis, when the patient’s sweat secretion has returned to normal, but not more often than every 12 weeks. There is some evidence for a cumulative effect of repeat doses so the time of each treatment for a given patient should be assessed individually.

**Children:** The safety and effectiveness of the product in the treatment of axillary hyperhidrosis in children have not been demonstrated.

**Method of administration:** When treating axillary hyperhidrosis, Botulinum Toxin Type A-Hemagglutinin Complex® is reconstituted with sodium chloride solution B.P. (0.9% w/v) to yield a solution containing 200 units per ml and it is administered by intradermal injection as described above.
4.3 CONTRAINDICATIONS

The product is contraindicated in individuals with known hypersensitivity to any of its components.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported (see section: Undesirable Effects). 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 dose possible and by not exceeding the maximum recommended dose.

Very rare cases of death, occasionally in the context of dysphagia, pneumopathy (including but not limited to dyspnœa, respiratory failure, respiratory arrest) and/or in patients with significant asthenia have been reported following 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.

Botulinum Toxin Type A-Hemagglutinin Complex 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.

Botulinum Toxin Type A-Hemagglutinin Complex should only be used with caution and under close medical supervision in patients with clinical or sub-clinical evidence of marked defective neuro-muscular transmission (e.g. myasthenia gravis). Such patients may have an increased sensitivity to agents such as Botulinum Toxin Type A-Hemagglutinin Complex, which may result in excessive muscle weakness.

The recommended posology and frequency of administration for Botulinum Toxin Type A-Hemagglutinin Complex must not be exceeded.

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

Botulinum Toxin Type A-Hemagglutinin Complex must not be used to treat spasticity in patients who have developed a fixed contracture.

For the treatment of spasticity associated with cerebral palsy in children, Botulinum Toxin Type A-Hemagglutinin Complex should only be used in children 2 years of age or over.

As with any intramuscular injection, Botulinum Toxin Type A-Hemagglutinin Complex should only be used where strictly necessary in patients with prolonged bleeding times, or infection/inflammation at the proposed site(s) of injection.
Botulinum Toxin Type A-Hemagglutinin Complex should only be used to treat a single patient, during a single session. Any unused product remaining should be disposed of in accordance with Special Precautions for Disposal and Handling. Specific precautions must be taken during the preparation and administration of the product and the inactivation and disposal of any unused reconstituted solution.

This product contains a small amount of human albumin. The risk of transmission of viral infection cannot be excluded with absolute certainty following the use of human blood or blood products.

Antibody formation to botulinum toxin has been noted rarely in patients receiving Botulinum Toxin Type A-Hemagglutinin Complex. Clinically, neutralizing antibodies might be suspected by a substantial deterioration in response to therapy and/or the need for consistent use of increased doses.

**4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**

The effects of botulinum toxin may be potentiated by drugs interfering either directly or indirectly with neuromuscular function and such drugs should be used with caution in patients treated with botulinum toxin.

**4.6 PREGNANCY AND LACTATION**

There are limited data from the use of *Clostridium botulinum* toxin type A – haemagglutinin complex in pregnant women. Animal studies do not indicate any direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development other than at high doses causing maternal toxicity (see Preclinical Safety section).

Botulinum Toxin Type A-Hemagglutinin Complex 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.

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

**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**

*Information included in section 4.8 is only relevant if the indication is approved.*
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**

*Nervous system disorders*
- Rare: Neuralgic amyotrophy

*Skin and subcutaneous tissue disorders*
- Uncommon: Itching
- Rare: Skin rashes

*General disorders and administration site conditions*
- Common: Generalised weakness, Fatigue, Flu-like syndrome and Pain / Bruising at injection site

**Adult spasticity of the leg post-stroke**
The following adverse events were observed in patients treated with Botulinum Toxin Type A-Hemagglutinin Complex for poststroke spasticity of the leg in adults.

*Gastrointestinal disorders*
- Common: Dysphagia

*Musculoskeletal and connective tissue disorders*
- Common: Leg muscle weakness

*Renal and urinary disorders*
- Uncommon: Urinary incontinence

*General disorders and administration site conditions*
- Common: Abnormal gait

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

**Adult spasticity of the arm post-stroke**
The following adverse events were observed in patients treated with Botulinum Toxin Type A-Hemagglutinin Complex for poststroke spasticity of the arm in adults.

*Gastrointestinal disorders*
- Common: Dysphagia

*Musculoskeletal and connective tissue disorders*
- Common: Arm muscle weakness

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

**Local symptomatic treatment of spasticity affecting the upper and/or lower limb in adults:**
The following adverse events were observed in patients treated with Botulinum Toxin Type A-Hemagglutinin Complex® for the treatment of spasticity of the lower limb in adults.

*Gastrointestinal disorders*
- Common: Dysphagia

*Musculoskeletal and connective tissue disorders*
- Common: Leg muscle weakness

*Renal and urinary disorders*
- Uncommon: Urinary incontinence
The following adverse events were observed in patients treated with Botulinum Toxin Type A-Hemagglutinin Complex® for the treatment of spasticity of the upper limb in adults.

**Gastrointestinal disorders**
- Common: Dysphagia

**Musculoskeletal and connective tissue disorders**
- Common: Arm muscle weakness

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

The following adverse events were observed in patients treated with Botulinum Toxin Type A-Hemagglutinin Complex® for the treatment of spasticity of both the lower and upper limbs in adults.

**Gastrointestinal disorders**
- Common: Dysphagia

**Musculoskeletal and connective tissue disorders**
- Common: Leg muscle weakness, Arm muscle weakness

**Renal and urinary disorders**
- Uncommon: Urinary incontinence

**General disorders and administration site conditions**
- Common: Abnormal gait

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

**Paediatric leg spasticity due to cerebral palsy**
The following adverse events were observed in paediatric patients treated with Botulinum Toxin Type A-Hemagglutinin Complex for leg spasticity due to cerebral palsy.

**Gastrointestinal disorders**
- Common: Diarrhoea

**Musculoskeletal and connective tissue disorders**
- Common: Leg muscle weakness, Muscle Pain

**Renal and urinary disorders**
- Common: Urinary incontinence

**General disorders and administration site conditions**
- Common: Abnormal gait

**Injury, poisoning and procedural complications**
- Common: Accidental injury due to falling

Accidental injury due to falling and abnormal gait may have been due to overweakening of the target muscle(s) and / or the local spread of Botulinum Toxin Type A-Hemagglutinin Complex to other muscles involved in ambulation and balance.

**Spasmodic torticollis**
The following adverse events were observed in patients treated with Botulinum Toxin Type A-Hemagglutinin Complex® for spasmodic torticollis.
Nervous system disorders
  Common: Headache, Dizziness, Facial Paresis
Eye disorders
  Common: Blurred vision, Visual acuity reduced
  Uncommon: Diplopia, Ptosis
Respiratory, thoracic and mediastinal disorders
  Common: Dysphonia, Dyspnoea
  Rare: Aspiration
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.

Blepharospasm and hemifacial spasm

The following adverse events were observed in patients treated with Botulinum Toxin Type A-Hemagglutinin Complex® for blepharospasm and hemifacial spasm.

Nervous system disorders
  Common: Facial muscle weakness
  Uncommon: Facial paralysis
Eye disorders
  Very common: Ptosis
  Common: Diplopia, Dry eyes, Tearing
  Rare: Ophthalmoplegia
Skin and subcutaneous tissue disorders
  Common: Eyelid oedema
  Rare: Entropion

Side effects may occur due to deep or misplaced injections of Botulinum Toxin Type A-Hemagglutinin Complex temporarily paralysing other nearby muscle groups.

Axillary hyperhidrosis
The following adverse events were observed in patients treated with Botulinum Toxin Type A-Hemagglutinin Complex for hyperhidrosis.

Nervous system disorders
  Uncommon: Dizziness, Headache, Paraesthesia, Involuntary muscle contractions of the eyelid
Vascular disorders
  Uncommon: Flushing
Respiratory, thoracic and mediastinal disorders
  Common: Dyspnoea
  Uncommon: Epistaxis
**Skin and subcutaneous tissue disorders**
- Common: Compensatory sweating

**Musculoskeletal and connective tissue disorders**
- Common: Pain in the shoulder, upper arm and neck, Myalgia of the shoulder and calf

**Post-marketing experience**

The profile of adverse reactions reported to the company during postmarketing use reflects the pharmacology of the product and those seen during clinical trials. There have been sporadic reports of hypersensitivity.

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).

**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 the 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.