HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

6 September 2006

New examination of the medicinal product

Botox 100 units, Allergan, powder for solution for injection
Box of 1 vial of powder, (CIP code: 562 088-8)

Applicant: Allergan

Botulinum toxin type A

List I
Medicine subject to restricted prescription: for hospital use only

Date of French Marketing Authorisation: 22 August 2000
Latest clinical amendment (extension of indication): 01 August 2005

Reason for request: inclusion on the list of medicines approved for hospital use in the extended therapeutic indication *Symptomatic treatment of upper and/or lower limb spasticity (muscle hyperactivity).*

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
botulinum toxin type A

1.2. Indications

Adults
Local symptomatic treatment of upper and/or lower limb spasticity (muscular hyperactivity)

Adults and children over 12
- eye movement disorders: strabismus, recent oculomotor palsy, recent thyroid myopathy,
- blepharospasm
- hemifacial spasm
- spasmodic torticollis
- severe axillary hyperhidrosis not responding to topical treatment and with substantial psychological and social consequences.

Children aged 2 and over
Treatment of dynamic equinus foot deformity in children with spasticity caused by cerebral palsy. Medical treatment should form part of wider multidisciplinary care (including a neurologist, paediatrician, physical medicine and rehabilitation specialist, and orthopaedic surgeon).

N.B: Botox should be administered by specialist doctors experienced in using the toxin in these indications.

1.3. Dosage in the extended indication

The exact dosage and number of injection sites should be individually tailored according to the patient's body size, the number and position of the muscles involved, severity of spasticity, presence of local muscle weakness and patient response to previous therapy.

See SPC for average dose per muscle injected (based on controlled clinical trials). In clinical trials, the total dose per injection session did not exceed 360 U. The total dose should be divided between the different muscles selected.

The total maximum dose is usually 6 U/kg.

Method of administration

A 25, 27 or 30 gauge needle should be used for superficial muscles and a longer needle for deeper muscles.

Electromyographic guidance or nerve stimulation techniques may be useful in isolating the muscles concerned. Choosing several injection sites per muscle ensures that Botox is more uniformly distributed and is particularly useful for large muscles.

Clinical improvement in muscle hypertonia usually occurs within two weeks of injection. The maximum clinical effect generally appears four to six weeks after treatment. Injection sessions can be repeated if necessary, but should always be at least 3 months apart.

In clinical trials, the interval between two injection sessions was 12–16 weeks.

At repeat injection sessions, the dose of Botox and the choice of muscles to be injected may need to be modified according to the intensity and type of muscle spasticity.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification 2006

M : Musculo-skeletal system
03 : Muscle relaxants
A : Muscle relaxants, peripherally acting agents
X : Other muscle relaxants, peripherally acting agents
01 : botulinum toxin

2.2. Medicines in the same therapeutic category

Comparator medicines

Botulinum toxin type A:
- Dysport 500 Units (Speywood), powder for solution for injection (concurrent request for inclusion on the list of medicines approved for hospital use).

Botulinum toxin type B:
- Neurobloc, solution for injection, 5000 IU/mL.

2.3. Medicines with a similar therapeutic aim

Medicines indicated for certain types of spasticity:
- Dantrium (dantrolene), capsules
- Lioresal (baclofen), tablets and solution for intrathecal injection
- benzodiazepines (without Marketing Authorisation).

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The applicant submitted:
- four phase II trials (not considered in the opinion),
- a literature review covering 50 published articles from 1990 to 2004 on efficacy data for Botox in treating spasticity of the lower and upper limbs from various causes (stroke (14 studies), multiple sclerosis (6 studies), spinal cord or brain injury (8 studies) and various causes (22 studies)).

Of these 50 published studies, 6 were randomised controlled trials on management of spasticity in patients with stroke, multiple sclerosis, or spasticity due to various causes. These trials had design limitations, notably the small number of patients enrolled and the large number of endpoints.

They had different designs and were conducted in a total of 129 patients:
- 4 trials compared several Botox doses with placebo
- 1 trial compared Botox with phenol 5%
- 1 trial compared Botox + ankle taping with standard Botox injections.

All were double-blind trials (except for Reiter, 1998), lasting from 2 weeks to 3 months.

Muscle tone was measured using the Ashworth scale or the modified Ashworth scale (MAS)[1].

In 6 trials, range of motion (ROM), categorised as passive or active, was also measured, using a goniometer. Step length and gait analysis were also used to identify abnormal movements.

Post-stroke spasticity (Table 1)

Two randomised trials analysed botulinum toxin efficacy in stroke patients:

- One double-blind trial (Kirazli, 1998) compared the efficacy of Botox (n = 10) with that of phenol 5% (n = 10) in treating lower limb spasticity. The primary endpoint was the MAS score. There was a significant decrease in MAS score with Botox compared with phenol 5%:
  - at 2 weeks: 1.5 ± 0.5 (Botox) vs. 0.7 ± 0.7 (phenol) - $p<0.05$
  - at 4 weeks: 1.4 ± 0.5 (Botox) vs. 0.7 ± 0.7 (phenol) - $p<0.05$

  At 8 or 12 weeks, there was no difference in MAS score between Botox and phenol.
- The second randomised single-blind trial (Reiter, 1998) compared the efficacy of Botox 100 IU together with ankle taping (n = 9) with that of Botox alone at the usual dose (190–320 IU), using MAS and ROM scores. Since the experimental design made it impossible to quantify the effect of therapy, the Transparency Committee did not take these results into account.

Spasticity in multiple sclerosis (MS) (Table 2)

A double-blind placebo-controlled crossover trial (Snow, 1990) assessed the efficacy of Botox in 10 patients with upper and lower limb spasticity. There was a significant improvement in MAS score in the Botox group (a decrease from 7.9 ± 4.87 to 4.87 ± 4.31) compared with an increase from 6.8 ± 5.26 to 7.1 ± 4.77 in the placebo group: ($p = 0.009$).

Spasticity from various causes (Table 3)

Three randomised double-blind placebo-controlled trials (Richardson, 2000; Childers, 1996; Grazko, 1995) analysed the efficacy of Botox in patients with upper and lower limb spasticity from various causes (stroke, MS, brain injury, brain tumour, Parkinson's disease and spinal trauma).

Different criteria and scales were used to measure spasticity. Despite the shortcomings in design, two trials showed significant improvements in MAS scores: $p < 0.02$ in the Richardson trial and a gain of 2 points (p not specified) in the Grazko trial. The third trial (Childers, 1996) showed no significant difference between the two methods of administration used and no analysis versus placebo was carried out.

Spasticity related to spinal cord or brain injury

Eight other trials (5 open-label trials and 3 case studies) were submitted but the Transparency Committee did not take their results into account because they lacked a rigorous design.

3.2. Undesirable effects

Common undesirable effects reported in the clinical trials were pain at the injection site, pain in injected limbs, ecchymosis, hypertonia, and muscle weakness. Uncommon undesirable effects were joint pain, weakness, haemorrhage, hyperaesthesia, pain, depression, dermatitis, headache, insomnia, feeling faint, nausea, itching, and skin rash.

1 Ashworth scale definitions: 0 = No increase in muscle tone; 1 = Slight increase in muscle tone; 2 = More marked increase in muscle tone; 3 = Considerable increase in muscle tone; 4 = Affected part is rigid in flexion or extension.

Following cases of dissemination of botulinum toxin at a distance from the target muscle, all companies marketing botulinum toxin products will be asked for a European risk management plan.

3.3. Conclusion

Several trials have assessed the efficacy of BTX-A in treating spasticity of the lower limbs (5 trials) and the upper limbs (3 trials). One trial assessed spasticity of both the upper and lower limbs.

There was a statistically significant improvement in spasticity score in the groups treated with BTX-A compared with placebo or 5% phenol.

There are no trial data comparing Botox with other active comparator drugs (e.g. alcohol, dantrolene or baclofen).

The Transparency Committee regretted the lack of data to assess the contribution of BTX-A compared with or in combination with functional rehabilitation.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Spasticity is a disabling handicap that can impair quality of life and have serious consequences for social and family life.

Botox is a symptomatic therapy.

It is a first-line medical therapy that should be used in combination with physiotherapy.

There are few alternative treatments available and there is a need for further therapy.

Public health benefit.

The seriousness of spasticity lies in the functional and psychosocial handicap it creates.
It is not possible to quantify the burden on public health because the impact of spasticity varies and there are no epidemiological data available.
Improving handicap is a public health priority. As existing treatments do not provide satisfactory results, there is an important treatment requirement in terms of public health.
However, the data available are not sufficient to quantify the expected impact of botulinum toxin on the quality of life of patients with spasticity, even in the short term. Its expected long-term impact cannot be predicted because of the lack of long-term studies.
Botox is therefore not likely to benefit public health in this indication.

The efficacy/safety ratio is limited.

The actual benefit of Botox in the new indication is substantial.

4.2. Improvement in actual benefit

The therapeutic benefit of Botox in current therapy for upper and/or lower limb spasticity cannot be estimated from the data available.

The Transparency Committee therefore considered that Botox does not offer any improvement in actual benefit (IAB V) in this new indication.

4.3. Therapeutic use [2]

Muscle spasticity is an increased contraction response to stretching and a pathological increase in muscle tone (hypertonia) due to overactivity of the afferent fibres. It can cause pain and spasms and result in functional impaiment of the upper and lower limbs.

Spasticity is caused by vascular, traumatic, infectious or degenerative damage to the central nervous system (brain or spinal cord). Central neurological pain may also occur under these conditions, so spasticity and central neuropathic pain often occur together.

Muscle spasticity requires treatment when it causes problems. From the functional point of view, it can be a handicap or, in some patients, a means of compensating for motor deficit. The therapist must weigh up the expected benefit in terms of pain reduction and consequences for gross motor function. Management depends on the clinical picture, the treatments available, and the consequences, depending on whether the functional handicap is diffuse or local and how serious it is.

Rehabilitation techniques that encourage muscle stretching and which can be combined with the use of splints and plaster casts to position the limb should be the first-line therapy.

Any drug therapy should always be combined with physiotherapy. In localised spasticity, the muscles involved should be treated locally. The methods are:

- injection of botulinum toxin in the muscle
- nerve block (e.g. alcohol, phenol)
- intrathecal baclofen.

In all cases, treatment aims to induce a localised decrease in muscle activity in order to improve motor function, and reduce the handicap and functional problems due to spasticity.

In patients with diffuse lesions, antispastic products such as baclofen, dantrolene, tizanidine (Temporary Authorisation for Use) or benzodiazepines (outside the terms of the Marketing Authorisation) may be proposed. In extreme cases, central neurostimulation or destructive surgery (Dorsal Root Entry Zone (DREZ) lesion, cordotomy) could be considered.

Botulinum toxin (Botox) should be administered by specialists with experience in the use of the drug in these indications. Botulinum toxin injection is a reversible, adaptable local therapy.

4.4. Target population

The target population is that of patients with upper and/or lower limb spasticity of diverse origin (e.g. stroke, MS, brain injury, spinal cord injury or Parkinson's disease). It cannot be estimated on the basis of the data available.

4.5. Transparency Committee recommendations

The Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services for the extended indication and at the dosages given in the Marketing Authorisation.

2 Fletcher D, *"Spasticité et douleur", Evaluation et traitement de la douleur*, SFAR 2003, p 125-133.

ANNEX

Table 1. *Post-stroke spasticity*

Author - Year	Objectives	Methodology	Efficacy	Safety
Kirazli[3] *et al* 1998	Assessment of the efficacy of BTX-A compared with phenol in treating spasticity of the plantar flexor and invertor muscles in poststroke patients.	• Randomised, double-blind trial: - n = 20 (3–12 months after stroke), - 12 weeks. • BTX-A 400 U (n = 10), phenol 5% (n = 10). • Primary endpoints: - passive and active ankle ROM, - brace wear scale, - MAS, - gait velocity, - duration of clonus, - overall spasticity assessment scale.	• ROM and brace wear scale: no statistical data available. • MAS: decreased spasticity with BTX-A vs. phenol at weeks 2 and 4 ($p < 0.05$), NS at weeks 8 and 12. • Gait velocity: significant improvement with BTX-A vs. phenol. • Duration of clonus: decrease with BTX-A vs. phenol at week 2 ($p < 0.05$), NS at weeks 4, 8 and 12. • Overall spasticity: improvement with BTX-A vs. phenol at weeks 2, 4 and 8 ($p < 0.05$), NS at week 12.	2 patients given BTX-A reported moderate discomfort on injection and 30% of patients given phenol 5% had dysesthesia which interfered with walking.
Reiter[4] *et al* 1998	Assessment of combined efficacy of low-dose BTX-A and ankle taping compared with traditional Botox therapy in poststroke patients with equinovarus.	• Randomised single-blind controlled trial: - n = 18 (mean time elapsed between stroke and treatment 22 months), - 3 months. • Group A: BTX-A 190–320 U in the gastrocnemius, soleus, tibialis posterior, extensor digitorum longus and extensor hallucis longus (n = 9). • Group B: BTX-A 100 U in the tibialis posterior + ankle taping in eversion for 3 weeks (n = 9). • Primary endpoints: - active and passive ankle ROM, - MAS, - gait velocity and step length.	• ROM: difference in favour of group A seen in dorsiflexion ($p < 0.05$). • No difference seen in other parameters. • MAS: decrease of at least 1 point on the scale in both groups compared with baseline.	Pain at injection site in 2 patients in group A and 1 patient in group B. No undesirable systemic effects.

BTX-A: botulinum toxin A

3 Kirazli *et al*., "Comparison of phenol block and botulinus toxin type A in the treatment of spastic foot after stroke", Am. J. Phys. Rehabil 1998; 77: 510-515.
4 Reiter *et al*., "Low-dose botulinum toxin with ankle taping for the treatment of spastic equinovarus foot after stroke", Arch. Phys. Med. Rehabil 1998;79: 532-535.

Table 2: Spasticity in multiple sclerosis

Author - Year	Objectives	Methodology	Efficacy	Safety
Snow[5] *et al*. 1990	Assessment of the efficacy and safety of BTX-A therapy for spasticity of the lower limbs (adductors) in patients with multiple sclerosis.	• Randomised, double-blind placebo-controlled crossover trial: – n = 10 (mean duration of disease 18.2 years). – 12 weeks. • Intramuscular injection of: - BTX-A in the adductor brevis (100 U), adductor longus (100 U) and adductor magnus (200 U), - saline solution. • Primary endpoints: - MAS for adductors, - spasm frequency score, - hygiene and care score.	• MAS: improvement with BTX-A (mean 7.9 ± 4.87 to 4.87 ± 4.31) vs. placebo (6.8 ± 5.26 to 7.1 ± 4.77); p = 0.009. • Frequency of spasms: NSD • Hygiene and care score: improvement with BTX-A vs. placebo (p = 0.02).	No secondary effects seen with BTX-A during treatment.

Table 3: Spasticity from various causes

Author - Year	Objectives	Methodology	Efficacy	Safety
Richardson[6] *et al*., 2000	Assessment of the efficacy of BTX-A therapy on upper or lower limb hypertonia in patients with a variety of conditions: following stroke (n = 23), brain injury (n = 12), incomplete spinal cord injury (n = 6), tumour (n = 5), CP (n = 3), anoxic episodes (n = 3).	• Randomised, double-blind placebo-controlled trial: - n = 52 (time post-trauma: 35 months), - 12 weeks. • Intramuscular injection of BTX-A in the upper limbs (mean 141 U; doses 30-305 U (n = 16)) and lower limbs (mean 285 U; doses 75-500 U (n = 11)), or placebo (n = 16 and n = 9). • Primary endpoints: - MAS, - PROM, - subjective rating of problem severity, (Rivermead), - time to walk 10 metres, - goal attainment scale score.	• Statistical tests were conducted on the sums of mean scores at weeks 3–12. No test available for all stages of analysis. • MAS: improvement with BTX-A vs. placebo on mean score (p < 0.02). • ROM: improvement with BTX-A vs. placebo on mean score (p < 0.03).	Pain at injection site in 4 patients in BTX- A group.

5 Snow *et al*., Treatment of spasticity with botulinum toxin: A double-blind study, Ann Neurol 1990;28:512-515.
6 Richardson *et al*. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults J Neurol Neurosurg Psychiatry 2000;69:499-506.

Childers[7] *et al*., 1996	Comparison of two Botox® injection techniques in the lower limb in patients with hemiplegia following stroke (n = 12), brain tumour (n = 1) or brain injury (n = 2).	• Randomised, double-blind placebo-controlled trial: - 17 patients with spasticity, - 5 weeks. • Intramuscular injection of Botox® 50 U into the medial or lateral gastrocnemius, either proximally (group I) or more distally (group II). Placebo injected at alternate sites to ensure the double blind. • <u>Endpoints</u>: - Fugl-Meyer, - MAS, - ROM, - time to walk 15 metres.	• No significant difference seen between the two groups for: - Fugl-Meyer score, - MAS score, - walking time. • ROM results not available.	No undesirable effects reported.
Grazko[8] *et al*., 1995	Assessment of the efficacy of BTX-A in patients with spasticity of the upper limbs (n = 4) and lower limbs (n = 8) following stroke (n = 3), MS (n = 5), perinatal hypoxia (n = 1) or brain injury (n = 3).	• Randomised, double-blind crossover trial, BTX-A vs. placebo: - n = 12, - examination 2 weeks post-injection and follow-up until return to initial state. • BTX-A dose 25–250 U (mean 138 U) or placebo. • <u>Primary endpoint</u>: - MAS.	• MAS: significant improvement (p not specified) of 2 points.	No data available.

7 Childers *et al*., Comparison of two injection techniques using botulinum toxin in spastic hemiplegia Am J Phys Med Rehabil 1996;75: 462-469.
8 Grazko *et al*. Botulinum toxin A for spasticity, muscle spasms, and rigidity. Neurology 1995;45: 712-717.