



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

13 January 2010

BOTOX 50 UNITS ALLERGAN, powder for solution for injection
Bottle of powder, Box of 1 (CIP code: 370 831-4)

BOTOX 100 UNITS ALLERGAN, powder for solution for injection
Bottle of powder, Box of 1 (CIP code: 562 088-8)

BOTOX 200 UNITS ALLERGAN, powder for solution for injection
Bottle of powder, Box of 1 (CIP code: 370 832-0)

Applicant: ALLERGAN

Botulinum toxin type A

ATC Code: M03AX01

List I

Medicinal product subject to restricted prescription: reserved for hospital use.

Date of (national) Marketing Authorisation:

BOTOX 100 units: 22/08/2000

BOTOX 50 and 200 units: 22/02/2006

Latest clinical amendment (extension in children over 2 years of age): 24/09/2009

Reason for request: inclusion on the list of medicines approved for use by hospitals and various public services in the extension of the therapeutic indication: **In children over 2 years of age** “*Local symptomatic treatment of spasticity (muscle hyperactivity) of the upper and/or lower limbs*”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Botulinum toxin type A

1.2. Indications

“Adults and children over 12 years of age:

- oculomotor disorders: strabismus, recent oculomotor paralysis, recent thyroid myopathy,
- blepharospasm,
- hemifacial spasm,
- spasmodic torticollis,
- Severe axillary hyperhidrosis which has not responded to local treatment resulting in a major psychological and social impact.
- Local symptomatic treatment of spasticity (muscle hyperactivity) of the upper and/or lower limb.

Children aged 2 years and over:

Old indication (included in the new indication):

- Treatment of dynamic equinus foot deformity in children with spasticity due to cerebral palsy

New indication:

- Local symptomatic treatment of spasticity (muscle hyperactivity) of the upper and/or lower limbs.

In children, injections of botulinum toxin must be administered by specialist doctors with substantial paediatric experience. This drug therapy must be part of an overall multidisciplinary care approach (including neurologist, paediatrician, physical medicine and rehabilitation, orthopaedic surgeon, etc.) and combined with rehabilitative care.

N.B.: BOTOX must be administered by specialist doctors with the proper experience of the use of the toxin in these indications.”

1.3. Dosage in the extension of the indication

“1) Preparation of the product

Prepare a solution in a dilution appropriate to the dosage (cf. Instructions for use, handling, and disposal).

2) Posology and method of administration

Reconstituted BOTOX is injected using a sterile, 27 or 30 gauge needle of a length appropriate to the target muscles. Localisation of the appropriate muscles with electromyographic guidance or nerve stimulation techniques may be useful.

The exact dosage and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. In the clinical trials, doses per muscle, of 0.5 to 2.0 units/kg body weight for the upper limb and 2.0 to 4.0 units/kg body weight for the lower limb were administered at each treatment session.

Do not exceed the recommended initial dosage at the start of the treatment.

In the treatment of talipes equinus, two injections are administered into each of the heads - medial (internal) and lateral (external) - of the affected gastrocnemius (gemellus) muscle.

- o In hemiplegia, the initial recommended dose is 4 units per kg injected into the affected limb.

- o In diplegia, the initial recommended dose is 6 units per kg, divided between the two affected limbs.

The initial recommended dose should be strictly adhered to particularly in children:

- presenting associated comorbidities, particularly those involving swallowing or respiratory disorders,
- in whom the muscles to be treated are not highly developed,
- who require injections at many sites,
- who are given injections under general anaesthesia.

As guidance, the table below provides instructions regarding the injection of BOTOX in the treatment of spasticity in children aged 2 years and over.

In all cases, when selecting the dose, an individual evaluation of the risk/benefit ratio must be undertaken in order to reduce the risk of adverse effects, including the risk of toxin spread distant from the administration site (see sections 4.4 and 4.8). Depending on the response to the previous treatment, the dose may, with extreme caution, be increased above the initial recommended dose, though, the maximum dose per session stated above must not be exceeded. The dose and the treatment plan must be re-evaluated if adverse effects occur.

Children aged 2 years and over (muscles cited as a rough guide)	Dose per muscle (U/kg)	Maximum dose per session
Muscles of upper limb: Biceps brachii, brachialis, brachioradialis Pronator quadratus Pronator teres Flexor carpi ulnaris/radialis Flexor pollicis longus/brevis/opponens Adductor pollicis Flexor digitorum profundis/superficialis	1-2 0.5-1 1-2 1-2 0.5-1 0.5-1 1-2	15 U/kg or 350 U or 50 U per site
Muscles of lower limb: Adductor longus/brevis/magnus Biceps femoris, semitendinosus, semimembranosus, sartorius Gastrocnemius Soleus	2-4 2-4 2-4 2-3	

Clinical improvement generally occurs within two weeks of the injection session. Injection sessions should be repeated according to the duration of the clinical effect. They must be at least 3 months apart. With an appropriate dosage it should be possible to obtain an interval of at least 6 months between sessions.

In the event of treatment failure after the first session, i.e. absence, at one month after injection, of significant functional improvement from baseline, the following actions should be planned:

- clinical evaluation, ideally by electromyographic examination in a specialised setting, of the toxin action on injected muscle,
- analysis of the causes of failure:
 - o not accurate selection of muscles to be injected (evaluation of soleus role),
 - o insufficient dosage,
 - o poor injection technique,
 - o appearance of fixed contracture,
 - o increased weakness of antagonist muscles,
- re-evaluation of the rationale of botulinum toxin type A treatment (see Special warnings and precautions for use),

- in absence of any adverse effects following the first treatment session, instigate a second treatment session:

- o adjusting the dose, taking into account analysis of earlier treatment failure,
- o use electromyographic guidance, and
- o maintain a 3-month interval between the two treatment sessions.

After failure of second treatment session, there is no reason to continue treatment with botulinum toxin type A.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

M	: Musculoskeletal system
M03	: Muscle relaxants
M03A	: Muscle relaxants, peripherally acting agents
M03AX	: Other muscle relaxants, peripherally acting agents
M03AX01	: Botulinum toxin

2.2. Medicines in the same therapeutic category

Botulinum toxin type A:

- DYSPORT 500 Units SPEYWOOD, powder for solution for injection,
- XEOMIN, DL 50

Botulinum toxin type B:

- NEUROBLOC, solution for injection containing 5000 IU/ml,

2.3. Medicines with a similar therapeutic aim:

Products indicated in certain forms of spasticity:

- DANTRIUM (dantrolene), hard capsule,
- LIORESAL (baclofen) tablet and solution for intrathecal injection,
- ZANAFLEX (tizanidine), medicine with temporary authorisation for premarket use,

Local treatments: 50% alcohol, 5% phenol (without Marketing Authorisation).

Other comparators:

- surgery for spasticity (posterior rhizotomy, selective neurotomy, muscle-tendon or bone-joint surgery),
- rehabilitation: kinesitherapy, ergotherapy, physiotherapy.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The company provided two studies, the aim of which was to evaluate the efficacy of botulinum toxin A (BTX-A) in the treatment of spasticity of the lower limbs (1 study)/upper limbs (1 study):

- Study BTOX-9060-715, the aim of which was to compare the efficacy of BTX-A injection used alongside a rehabilitation programme¹ with the efficacy of this programme alone in terms of functional improvement of the upper limb in 30 children with cerebral palsy.
- The study by Koman et al. 2000², the aim of which was to compare the efficacy of BTX-A injection with that of placebo in terms of the improvement of walking in 114 children with cerebral palsy.

The company also submitted the results of an observational study, the aim of which was to evaluate the impact of treating spasticity with BTX-A injected into the spastic muscles of the lower limbs in children and the upper limbs in adults ("BOTULOSCOPE" study). Only the data from this study that relate to children will be described in this opinion.

3.1.1 Study BTOX-9060-715

Method: Randomised comparative study of BTX-A + rehabilitation (ergotherapy) versus rehabilitation + placebo, carried out in 30 children with congenital hemiplegic spasticity who were monitored for 12 weeks.

Inclusion criteria: children with moderate congenital hemiplegic spasticity without fixed muscle contracture (hypertonicity score of 1 to 3 on the MAS scale³).

Treatment:

- an injection of BTX-A 0.5 to 2 U /kg per muscle group treated (3 to 8 U/kg body weight/day) + ergotherapy, n=15,
- ergotherapy alone, n=15.

Primary endpoint: Functional evaluation of the affected upper limb using the Melbourne scale (Melbourne Unilateral Upper Limb Assessment) after 12 weeks' monitoring.

The Melbourne scale is based on the evaluation of 16 tasks covering familiarization with and objects handling (see Annexe 1). Each task being given a rating of 0 to 4. The score (%) is obtained using the following formula: $[\text{test score}/\text{maximum score (122)}] \times 100$. The tests last 30 min. This scale has been validated for children between 5 and 15 years of age with neurological deficit.

Note: This scale was not designed, and has not been validated, for children between 2 and 5 years of age.

1 One 1-hour session of individual ergotherapy per week

2 Koman et al. "Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial" J Pediatr. Orthop 2000;20:108-15.

3 Modified Ashworth Scale (MAS) definitions: 0 = no increase in muscle tone; 1 = slight increase in muscle tone; 2 = marked increase in muscle tone; 3 = considerable increase in muscle tone; 4 = limb rigid on flexion or extension.

RESULTS: Intention-to-treat analysis

Table 1: Functional evaluation of the affected upper limb using the Melbourne scale (Melbourne Unilateral Upper Limb Assessment).

	BTX-A (n=15)	Placebo (n=15)	Mean difference	p
Inclusion	69 ± 14	67 ± 14		
After 3 weeks	79 ± 11	66 ± 16	10.1 [3.58; 16.6]	0.002
After 12 weeks	83 ± 10	67 ± 13	12.9 [6.12; 19.86]	0.0001

Twelve weeks after BOTOX was administered, a significant improvement in upper limb function (evaluated with the Melbourne scale) was observed in the BTX-A group in comparison with placebo: 83 ± 10 versus 67 ± 13, mean difference 12.9 [6.12; 19.86], p = 0.0001. This improvement was observed starting at the 3rd week of treatment.

3.1.2 Study by Koman et al., 2000²

Method: Randomised double-blind comparative study of BTX-A versus placebo, carried out in 114 hemiplegic or diplegic children with dynamic equinus foot deformity and cerebral palsy (CP) who were monitored for 12 weeks.

Inclusion criteria: children (2 to 16 years of age) with dynamic equinus foot deformity on walking and hemiplegia or diplegia. Tetraplegic patients were not included in the study.

Treatment:

- BTX-A 4 U/kg in the hemiplegic children and 8 U/kg in the diplegic children, n=56
- Placebo, n=58.

Primary endpoint: Percentage of responders, defined as those who, at week 12, show an improvement > 2 of own composite gait-pattern score, evaluated using the modified Physician Rating Scale (PRS). This scale is based on evaluation of 6 functional aspects of gait pattern over a distance 6 metres (see Annexe 2).

RESULTS:

After 12 weeks of treatment, the percentage of responders was significantly higher in the BTX-A group than in the placebo group: 55% (28/51 patients) versus 32% (18/55 patients), absolute difference 23%, p = 0.022.

3.1.3 “Botuloscope” study

This clinical and economic observational study of limb spasticity treatment with botulinum toxin was established as part of the STIC program (soutien aux innovations thérapeutiques et coûteuses coûteuses [costly therapeutic innovations support]) funded by Ministry of Health.

Method: Observational study of a consecutive series of 704 patients (395 adults and 309 children) with disabling spasticity and monitored for 12 months.

Note: the inclusion target was initially set at 430 children and 530 adults so that, after 12 months, 70% of the patients would have reached the goal defined at the pre-injection visit.

Inclusion criteria:

Patients qualifying for targeted treatment for disabling spasticity:

- focal spasticity of children with CP between 2 and 16 years of age (talipes equinus),
- spasticity of the upper limbs in adults (> 16 years of age) who are hemiplegic following a CVA,
- other disabling focal spasticities,

Within the framework of initial injection or reinjection of BTX-A.

Data collection: A specific case report form was created for each patient. The data were collected prospectively by a CRA and captured anonymously on a secure website.

Data analysis: The adults and children data were analysed separately and as *per protocol*.

Analysis of clinical benefit: Before first injection, treatment goals were defined between physicians and patients and prioritized (goal No. 1 and so on); they were then classified in three subject areas: “functional aspects”, “independence and quality of life”, and “care management”.

The improvement in the goals is defined by scores median and quartiles obtained on VAS; evaluation priority was given to goal No. 1 as defined by doctors and patients.

Treatments:

BOTOX was administered in 68% of the 509 injections and DYSPORT in 32%. The mean injected dose was 10.4 ± 5 U/kg for BOTOX and 26.6 ± 14 U/kg for DYSPORT.

Results: See Table 2, *per-protocol* analysis

Of the 282 patients included:

- 247/282 (88%) had cerebral palsy,
- 61/282 were hemiplegic, 155/282 (55%) diplegic, and 63/282 (22%) quadriplegic/triplegic.

The mean age was 6.3 ± 2.8 years (50% over 6 years of age).

Table 2: The improvement in goal No. 1 was evaluated at 1, 3 and 12 months on the VAS (median [Q1-Q3]).

Goal area	After 1 month	After 3 months	After 12 months
Functional aspects (n=209)	5 [3-7]	5 [3-7]	6 [4-8]
Independence and quality of life (n=32)	4 [0 -6]	5.85 [3-7]	6 [3-8]
Care management (n=26)	7 [5-8]	7.5 [5-8]	7.5 [3-8]

After 12 months' monitoring, functional aspects and independence and quality of life had improved by 60% in 50% of the patients evaluated; care management had improved by 75%.

3.2. Adverse events

In BTOX-9060-715 study, adverse events were observed in 3/15 patients (20%) of the BTX-A group:

- a decreased ability to extend the index finger in 2 patients,
- pollakiuria in 1 patient.

No adverse effect was observed in the placebo group.

In Koman et al., study, adverse events were observed in 15/145 patients (10%): 12/72 (17%) in the BTX-A group versus 3/73 patients (7%) in the placebo group. The commonest adverse events were:

- claudication: 2/72 patients versus 0,
- leg/calf pain: 2/72 patients versus 0,
- fall: 2/72 versus 1/73.

In “botuloscope” study, adverse events were reported in 35% of the injections (177/509). The commonest adverse effects were:

- weakness: 72/177 (41%),
- pain: 67/177 (38%),
- enuresis: 18/177 (10%).

3.3. Conclusion

The efficacy and tolerability of BTX-A were evaluated versus placebo in two randomised studies, in combination with a rehabilitation programme in one and without a rehabilitation programme in the other, which were carried out in children with cerebral palsy (BTOX-9060-715 study and Koman et al., study).

In BTOX-9060-715 study, 12 weeks after administration, upper limb function (evaluated using Melbourne scale) had improved significantly in the BTX-A group + ergotherapy (83 ± 10) in comparison with the ergotherapy alone treated group (67 ± 13), the mean difference being 13 [6.1; 19.9], $p = 0.0001$. This improvement was observed from the 3rd week of treatment.

In Koman study, 12 weeks after administration, the percentage of patients responding, defined as those showing improvement of > 2 in their composite gait-pattern score, evaluated using modified "Physician Rating Scale (PRS)", was significantly higher in the BTX-A group (55%) than in the placebo group (32%), the absolute difference being 23%, $p = 0.022$.

The adverse effects reported more frequently in the BTX-A group than in the placebo group were: claudication, pain, fall, weakness, and pollakiuria.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Spasticity is a disabling handicap which adds to that of the underlying aetiology and which can impair quality of life and have major knock-on effects socially and on the family.

These proprietary products fall under the category of symptomatic treatment.

This medicinal product is a first-line therapy to be used alongside kinesitherapy.

There are few treatment alternatives and they are administered systemically. There is a therapeutic need.

Public health benefit:

The seriousness of spasticity is due to the functional and psychosocial handicap that it causes. The public-health burden of this disease is small in this population (children between 2 and 12 years of age).

Amelioration of handicap is a public-health priority. As the results of existing treatments are not satisfactory, there is a therapeutic need that is important in public-health terms.

However, on the basis of the available data, the expected impact of BOTOX on morbidity and mortality and quality of life is hard to quantify, even in the short term. The impact on the care system is not documented.

Consequently, the public-health benefit of BOTOX in this indication is not quantifiable.

The efficacy/adverse effect ratio is modest.

The actual benefit of these proprietary products in this new indication is substantial.

4.2. Improvement in actual benefit

BOTOX (botulinum toxin type A) products provide a minor improvement in actual benefit (IAB IV) in terms of efficacy in the treatment of spasticity (muscle hyperactivity) of the upper and/or lower limbs in children aged 2 years and over.

4.3. Therapeutic use^{4,5}

Muscle spasticity is an increased contractile response to stretching and a pathologically increased muscle tone (hypertonicity) due to hyperactivity of the afferent fibres. It can cause pain and spasms and lead to functional impotence of the upper and/or lower limbs.

The causes of spasticity are central nervous system disorders of a vascular, traumatic, infectious, or degenerative type. There is frequently a connection between spasticity and central neuropathic pain.

Spasticity often has an adverse impact on motricity and the locomotor apparatus, but it can be non-troublesome or even useful. Not every spastic patient always requires treatment.

Spasticity must be analysed as a symptom using a standard approach, no matter what its aetiology is. Any aggravating cause, or nociceptive stimulus, must be investigated.

The goal of treatment is to induce a local decrease in muscle activity in order to improve motor function and reduce the handicap and functional disturbance caused by the spasticity.

Drug therapy, when considered, must always be used in conjunction with kinesitherapy.

Consideration of first-line treatments depends on the local or diffuse nature of the spasticity and on the aetiology.

Drug treatments for spasticity in children (see Annexe 3):

Intramuscular botulinum toxin A can be used as a first-line treatment for local or multifocal spasticity (professional consensus). It is a reversible and adjustable local treatment.

The only oral treatment with Marketing Authorisation is baclofen (from 6 years of age). The data do not permit recommendation of its use, however Diazepam is frequently used, in spite of the absence of Marketing Authorisation in this indication. In view of its sedative effect, it needs to be used with care and for a short period only (professional consensus).

Intrathecal baclofen is effective on spasticity. It is recommended chiefly in spinal cord injury and multiple sclerosis (Grade A) in patients whose lower-limb spasticity is widely distributed, sometimes spreading to the trunk (Grade A).

Alcohol and phenol are not the first-line treatment except in certain cases of particularly diffuse and troublesome spasticity, in which they can sometimes be used alongside another local treatment (botulinum toxin) (Professional consensus). In children under 10 years of age, extreme caution is recommended.

Botulinum toxin A (BOTOX) must be administered by specialised doctors with experience of its use in these indications.

4.4. Target population

The target population is children aged 2 years and over with spasticity of the upper and/or lower limbs of various aetiologies (CVA, MS, head injuries, spinal problems, cerebral palsy, etc.). It is not possible to estimate this target population on the basis of the available data.

Only the population of patients with dynamic equinus foot deformity in children with spasticity due to cerebral palsy is quantifiable in regard to the target population. It can be estimated from the following data.

4 Fletcher D, « Spasticité et douleur », Evaluation et traitement de la douleur, SFAR 2003, pages 125-133.

5 « Traitements médicamenteux de la spasticité » recommandations de bonne pratique, Afssaps June 2009

The target population is made up of children born with cerebral palsy (CP) who have unilateral spasticity that has resulted in equinus foot deformity.

The incidence of cerebral palsy (CP) is estimated at 2 per 1000 births⁶. According to INSEE [French National Institute for Statistics and Economic Studies] data, approximately 816,500 births were recorded in 2007. The number of children born with CP is thus around 1633 per year.

Roughly 85% of these children show spasticity¹³. Talipes equinus is generally unilateral; 35% of cases (expert opinion), or 485 children per year, are affected.

The duration of treatment covers the growth period, estimated at 10 years on average. On the basis of these data, the target population for BOTOX in children with dynamic equinus foot deformity would around 5000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the extension of the indication in patients over 2 years of age and at the dosage in the Marketing Authorisation.

6 Cans Ch. et al. « Epidémiologie de la Paralysie Cérébrale », Motricité Cérébrale 2005; 26:51-58

Annexe 1

Melbourne Assessment		
1. Reaching forwards	1.1	Range of movement
	1.2	Accuracy of movement
	1.3	Fluency of movement
2. Reaching forwards to an elevated position	2.1	Range of movement
	2.2	Accuracy of movement
	2.3	Fluency of movement
3. Reaching sideways to an elevated position	3.1	Range of movement
	3.2	Accuracy of movement
	3.3	Fluency of movement
4. Grasp of a pen		
5. Drawing grasp		
6. Release of a pen	6.1	Range of movement
	6.2	Quality of movement
	6.6	Accuracy of movement
7. Grasp of a pellet		
8. Release of a pellet	8.1	Range of movement
	8.2	Quality of movement
	8.3	Accuracy of movement
9. Manipulating a cube	9.1	Finger dexterity
	9.2	Fluency of movement
10. Pointing	10.1	Red square
	10.2	Green square
	10.3	Yellow square
	10.4	Blue square
11. Reach to brush from forehead to back of neck	11.1	Range of movement
	11.2	Fluency of movement
12. Palm to bottom	12.1	Range of movement
	12.2	Fluency of movement
13. Pronation/supination		
14. Hand to hand transfer		
15. Reach to opposite shoulder	15.1	Range of movement
	15.2	Accuracy of movement
	15.3	Fluency of movement
16. Hand to mouth and down	16.1	Range of movement
	16.2	Accuracy of movement
	16.3	Fluency of movement
	16.4	Speed of movement

Annexe 2

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Inclusion No.

2. Physicians Rating Scale - Lower limb (Koman - modified, Corry, Boyd)

			Left	Right
Knee position in midstance, in flexion	Severe > 15°	0		
	Moderate 10-15°	1		
	Mild < 10°	2		
	Neutral	3		
Knee position in midstance, recurvatum	Mild < 5°	2		
	Moderate 5-10°	1		
	Severe > 10°	0		
Initial contact	Toes	0		
	Forefoot	1		
	Foot-flat	2		
	Heel	3		
Foot contact at midstance	Toe/toe (equinus)	-1		
	Foot-flat/early heel rise	0		
	Foot-flat/no early heel rise	1		
	Occasional heel/foot-flat	2		
	Heel/toe (normal roll-over)	3		
Timing of heel rise	No heel contact	0		
	Before 25% stance (very early)	1		
	Between 25 and 50% (slightly early)	2		
	At terminal stance	3		
	No heel rise (after foot-flat, i.e. crouch)	0		
Hindfoot at midstance	Varus	0		
	Valgus	1		
	Neutral	2		
Base of support	Frank scissoring	0		
	Narrow base (poor knee clearance)	1		
	Wide base	2		
	Normal base (width of shoulders)	3		
Gait assistive devices	Walker (forward/posterior) with assistance	0		
	Walker (independent)	1		
	Crutches, sticks	2		
	None, independent for 10 m	3		
Overall change	Worse	-1		
	None (or first evaluation)	1		
	Better	2		

TOTAL (maximum score: 22 per side)

BOTULOSCOPE STUDY
20

Pre-injection consultation

Annexe 3
General principles of treatment for children with cerebral palsy (Afssaps [French Health
Product Safety Agency] – June 2009)

Children with cerebral palsy

General principles

- Avoid oral treatments
- Masso-kinesitherapy in all instances
- Appliances in all instances: daytime and/or night-time and/or postural
- Identify the muscle groups where the spasticity is:
 - most troublesome in regard to functional or non-functional goals
 - most harmful in regard to bone growth and prevention of orthopaedic deformities

Early first-line local botulinum toxin therapy for focal spasticity or a focal goal in the context of diffuse spasticity

1. Goals achieved

- Repeat every 3-6 months
- Monitoring and regular evaluation of orthopaedic, functional, and other goals

Goals not achieved

2. In treated groups

3. Because other groups involved

No retraction

- Repeat sooner, every 3 months
- Discuss :
 - . choice of muscles
 - . sites
 - . doses + increased
 - . injection technique

Possible retraction

- Discuss intensification : posture, appliance, cast, equinus reduction

1., 2., 3.

Goals
achieved

Goals not
achieved

1.

3.

- Discuss combination:
 - . alcohol/phenol
 - . oral treatment, if pain, discomfort afterwards:
- After > 6 years:
 - . intrathecal baclofen if weight > 30 kg
 - . spasticity surgery