HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 March 2011

XEOMIN 100 LD50 UNITS, powder for solution for injection
B/1 (CIP code: 571 886-0)

Applicant : MERZ PHARMA FRANCE

Clostridium Botulinum neurotoxin type A (150 kD), free of complexing proteins
ATC code: M03AX01

List I

Medicine for restricted prescription: reserved for hospital use

Date of Marketing Authorisation (mutual recognition, Referent Member State Germany): 8 January 2008
Date of the extension of indication: 20 January 2010
The medicinal product XEOMIN is the subject of a risk management plan.

Reason for request: Inclusion on the list of medicines approved for hospital use in the extension of indication “Treatment of post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist in adults”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient:

Clostridium Botulinum neurotoxin type A (150 kD), free of complexing proteins

1.2. Indications

"XEOMIN is indicated for the symptomatic treatment of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults.
TC Opinion of 19.03.2008: substantial actual benefit, IAB V / for other type A Botulinum toxins

New indication:
Treatment of post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist in adults"

1.3. Dosage and method of administration (in the new indication)

"**Post-stroke spasticity of the upper limb**
Reconstituted XEOMIN is injected using a suitable sterile needle (e.g. 26 gauge/0.45 mm diameter/37 mm length, for superficial muscles and a longer needle, e.g. 22 gauge/0.7 mm diameter/75 mm length, for deeper muscles). Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. Multiple injection sites may allow XEOMIN to have more uniform contact with the innervation areas of the muscle and is especially useful when larger muscles are injected.

The exact dosage and number of injection sites should be tailored to the individual patient based on the size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness.

In the management of post-stroke spasticity of the upper limb the following initial doses (units) were administered in the pivotal clinical trial:

Clinical Pattern Muscle	**Units**
Flexed wrist	
Flexor carpi radialis	50
Flexor carpi ulnaris	40
Clenched Fist	
Flexor digitorum superficialis	40
Flexor digitorum profundus	40
Flexed Elbow	
Brachioradialis	60
Biceps	80
Brachialis	50
Pronated Forearm	
Pronator quadratus	25
Pronator teres	40
Thumb-in-Palm	
Flexor pollicis longus	20
Adductor pollicis	10
Flexor pollicis brevis/Opponens pollicis	10

In the pivotal clinical trial, the minimum and maximum total doses were 170 U and 400 U, respectively.
For repeated treatments dosing should be tailored to the individual patient's need. The recommended dosage ranges per muscle are provided in the following table:

Clinical Pattern Muscle	**Units** (Range)	**Number of injection sites per muscle**
Flexed Wrist		
Flexor carpi radialis	25-100	1-2
Flexor carpi ulnaris	20-100	1-2
Clenched Fist		
Flexor digitorum superficialis	40-100	2
Flexor digitorum profundus	40-100	2
Flexed Elbow		
Brachioradialis	25-100	1-3
Biceps	75-200	1-4
Brachialis	25-100	1-2
Pronated Forearm		
Pronator quadratus	10-50	1
Pronator teres	25-75	1-2
Thumb-in-Palm		
Flexor pollicis longus	10-50	1
Adductor pollicis	5-30	1
Flexor pollicis brevis/Opponens pollicis	5-30	1

The maximum total recommended dosage is up to 400 units per treatment session.
Patients reported the onset of clinical effect 4 days after treatment. The maximum effect evaluated as an improvement of muscle tone was perceived within 4 weeks. In general, the treatment effect lasted 12 weeks. Reinjections should not be performed within intervals of less than 12 weeks.

<u>All indications</u>:
If no treatment effect occurs within one month after the initial injection, the following measures should be taken:
- Clinical verification of the neurotoxin effect on the injected muscle(s): e.g. an electromyographic investigation in a specialised facility;
- Analysis of the reason for non-response for which there are many possibilities, e.g. inaccurate location of the muscles intended to be injected, too low dose, inaccurate injection technique, fixed contracture, insufficient consideration of antagonist muscles' weakness, possible development of antibodies;
- Review of Botulinum neurotoxin type A treatment as an adequate therapy;
- If no adverse reactions have occurred during the initial treatment, an additional course of treatment can be performed under the following conditions: 1) dose adjustment with regard to analysis of the most recent therapy failure, 2) EMG-guidance, 3) the recommended minimum interval between the initial and repeat treatment is followed.

A treatment-naïve patient should be regarded as a primary non-responder in cases of first injection failure. It has not been investigated whether secondary non-response due to the development of antibodies is less frequent under XEOMIN therapy than under treatment with conventional preparations containing the Botulinum toxin type A complex. In cases of non-response, alternative therapies should be considered.

XEOMIN has not been studied in the paediatric population and is therefore not recommended in the paediatric age group until further data become available."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

M : Musculo-skeletal 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:
- BOTOX 50 U, 100 U and 200 U, powder for solution for injection
- DYSPORT 500 SPEYWOOD units, powder for solution for injection

2.3. Medicines with a similar therapeutic aim

Proprietary medicinal products indicated in certain forms of spasticity:
- NEUROBLOC (Botulinum toxin type B), solution for injection, 5000 IU/ml,
- DANTRIUM (dantrolene), capsule,
- LIORESAL (baclofen) tablet and solution for injection (for intrathecal administration).

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and tolerance of XEOMIN were evaluated in 2 double-blind randomised studies (1 study versus placebo and one study comparing two different doses of XEOMIN) and a noncomparative open follow-up study:

- study MRZ 0410-1, the aim of which was to compare the efficacy of XEOMIN with placebo in terms of the improvement in wrist spasticity at week 4, performed in 148 patients with post-stroke spasticity of the upper limb.
- study MRZ 0410-2 which consisted of open follow-up of the patients from study MRZ 0410-1,
- study MRZ 0607 the aim of which was to compare the efficacy and tolerance of two dilutions of XEOMIN in terms of the improvement in spasticity, performed in 192 patients with spasticity of the upper limb of various aetiologies.

Rehabilitation was not specifically evaluated in these studies; the patients included could continue their rehabilitation if this was regarded as "stabilised" at least two weeks before inclusion but this rehabilitation could not take place on the days on which the efficacy of the toxin was to be evaluated, so as not to interfere with the results.

3.1.1. Study MRZ 0410-1[1]

Method: randomised, double-blind comparative phase III study of XEOMIN versus placebo in 148 patients with post-stroke spasticity of the upper limb.

Inclusion criteria: Adult patients with more than six months' history of stroke with:

- focal spasticity of the flexor muscles of the wrist and fingers defined as a score ≥ 2 on the Ashworth scale[2],
- a score ≥ 2 (moderate) on the Disability Assessment Scale (DAS[3]) in one of the following 4 areas: hygiene, dressing, limb position and pain.

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Treatments: patients were randomised in two groups:

- XEOMIN, mean dose 307 U [80; 435]*, n = 73,
- Placebo, n = 75.

** According to the SmPC, "the maximum total dosage is 400 units per treatment session."*

Primary efficacy endpoint: percentage of responders after 4 weeks of treatment at the level of the wrist flexors; responders were defined by a reduction of at least one point in the Ashworth score[1] by comparison with the baseline.

Secondary endpoints, in particular : percentage of responders (wrist) at the final visit (between 13 and 21 weeks), percentage of responders (finger, thumb, elbow and forearm pronator).

RESULTS: *intention to treat* analysis *(cf. Table 1)*
The patients' characteristics were globally comparable on inclusion except for the patients' mean age (58.1 years in the XEOMIN group versus 53.3 years in the placebo group) and the

1 Kanovsky et al.« Efficacy and safety of botulinum neurotoxin NT 201 in poststroke upper limb spasticity. Clin Neuropharm 2009: 259-65.
2 Definition on the Ashworth scale: 0 = No increase in muscle tone; 1 = Slight increase in muscle tone; 2 = Marked increase in muscle tone through all the range of motion (ROM) but affected part easily moved; 3 = Considerable increase in muscle tone, passive movement difficult; 4 = Affected part rigid in flexion or extension.
3 Definition on the DAS: 0 = No disability, 1 = Mild disability, 2 = Moderate disability, 3 = Severe disability.

time for which patients had had spasticity (60.9 months versus 49.2 months), statistical analysis not available.

Table 1: Percentage of responders after 4 weeks of treatment: analysis of wrist flexion

	XEOMIN n = 73	**Placebo** n = 75	Odds ratio [95% CI] p
Percentage of responders (improvement of at least 1 point in the Ashworth score for the wrist)	68.5%	37.3%	**3.97 [1.90; 8.30]** **< 0.001**

After 4 weeks of treatment, the percentage of responders at the level of the wrist flexor was significantly higher in the XEOMIN group than in the placebo group: 68.5% versus 37.3%, OR = 3.97 [1.90; 8.30], p < 0.001.
The analysis at the termination study visit (between 13 and 21 weeks, secondary endpoint) confirmed these results: OR = 3.64 [1.41; 9.40], p = 0.007.

After 4 weeks of treatment, the percentage of responders was also significantly higher in the XEOMIN group than in the placebo group, for the other muscle groups treated (secondary endpoints), except for the forearm pronators:
- finger: OR = 3.41 [1.62; 7.20], p = 0.001,
- thumb: OR = 13.43 [2.28; 78.99], p = 0.004,
- elbow: OR = 3.16 [1.33; 7.51], p = 0.009,
- forearm pronators: OR 3.12 [0.97; 10.07], NS.

At the final visit (between 13 and 21 weeks), no significant difference was observed between the XEOMIN and placebo groups.

3.1.2. Study MRZ 0410-2: open follow-up study

The aim of this open follow-up study was to evaluate the efficacy and tolerance of repeated doses of XEOMIN.
It included 145/148 patients from study MRZ 0410-1 who were followed up for 48 to 69 weeks (mean duration of exposure 63.6 weeks ± 17.6).
During this study, patients received up to 5 injections (68% of patients received 4 injections) and efficacy was analysed 4 weeks after each one.
The Ashworth score improved significantly (p < 0.0001) compared to baseline for the first 4 injections in the five localisations studied (wrist, finger, thumb, elbow, forearm pronators). This effect was maintained until the fifth injection for the wrist, the fingers and the forearm pronators (p < 0.05) and until the fourth for the thumb and the elbow (p < 0.0001) but was not maintained at the fifth injection (NS).

3.1.3. Study MRZ 0607

Method: Randomized, single-blind study of the non-inferiority of XEOMIN 20 U/ml versus XEOMIN 50 U/ml, performed in 192 patients with upper-limb spasticity of various aetiologies.
Non-inferiority was accepted if the lower limit of the confidence interval for the difference in the percentage of responders did not exceed a limit set at -25%. A per protocol analysis was made.

Inclusion criteria: Patients more than 18 years of age with upper-limb spasticity at least 6 months post-stroke, head injury, multiple sclerosis, cerebral palsy or spinal cord lesion. Spasticity was defined by:
- a score of ≥ 2 on the Ashworth scale[1] for the flexor muscles of the wrist alone or combined with a score of ≥ 2 on the Ashworth scale[1] for the muscles of the elbow,
- a score of ≥ 2 (moderate) on the Disability Assessment Scale (DAS[2]) in one of the following 4 areas: hygiene, dressing, limb position and pain.

Treatments: patients were randomised in two groups:
- XEOMIN, 20 U/ml (n = 97),
- XEOMIN, 50 U/ml placebo (n = 95).

Primary efficacy endpoint: percentage of responders after 4 weeks of treatment; responders were defined by a reduction of at least one point in the DAS score compared to the level on inclusion for at least one of the 4 main therapeutic areas selected (hygiene 7.9%, dressing 23.6%, limb position 63% and pain 5.5%).

RESULTS: *per protocol* analysis
After 4 weeks of treatment, 63% of the group on XEOMIN 20 U/ml versus 52.4% of the group on XEOMIN 50 U/ml responded to the treatment (difference 10.6%, 95% CI [-4.4; 24.9]; since the lower limit of the confidence interval for the difference observed was -4.4 points, i.e. below the limit set in the protocol (-25%), the non-inferiority of XEOMIN 20 U/ml compared to XEOMIN 50 U/ml was accepted.

3.2. Adverse effects

During the study MRZ 0410-1, 41 patients had an adverse event: 21/73 patients (28.8%) in the XEOMIN group and 20/75 patients (26.7%) in the placebo group.

Over the 89 weeks (study MRZ 0410-1 then 0410-2), 61.2% of the patients had at least one adverse event, 12.2% of which were linked to the treatment.

During study 607, 73 patients had adverse events: 41/95 patients (42.7%) in the group on XEOMIN 50 U/ml and 32/97 patients (33.3%) in the group on XEOMIN 20 U/ml.

According to the SmPC, the most commonly adverse events observed in patients after stroke were: pain and haematoma at the injection site, muscle weakness.

Following the occurrence of cases in which the Botulinum toxin spread at a distance from the target muscle, a European risk management plan was put in place for all companies marketing proprietary medicinal products containing Botulinum toxin.

3.3. Immunogenicity

XEOMIN is a proprietary medicinal product containing purified Botulinum toxin A or neurotoxin free from complexing proteins.

Animal studies (Bluemel 2006, Jost 2007 and Eisele 2007) suggested a smaller immunogenic potential for XEOMIN compared to “conventional” Botulinum toxins (BOTOX, DYSPORT) which has not been confirmed clinically.

As with the other type A Botulinum toxins available on the market, the SmPC for XEOMIN states that “too frequent injection of Botulinum toxin may result in antibody formation which may lead to treatment resistance”.

3.4. Conclusion

The efficacy and tolerance of XEOMIN were evaluated in 2 double-blind randomised studies and one non-comparative follow-up study (MRZ 0410-2).

In study MRZ 0410-1, comparative versus placebo, the percentage of responders (reduction of at least one point in the Ashworth spasticity score at the level of the wrist flexors) after 4 weeks of treatment was higher in the XEOMIN group (at the maximum dose of 400 U) than in the placebo group: 68.5% versus 37.3%, OR 3.97 [1.90; 8.30], $p < 0.001$. These results

were confirmed between 13 and 21 weeks at the final visit (secondary endpoint): OR 3.64 [1.41; 9.40], p = 0.007.
After 4 weeks of treatment, the percentage of responders was also higher in the XEOMIN group than in the placebo group for the other localisations (secondary endpoints), except for the forearm pronators:

- finger OR 3.41 [1.62; 7.20], p = 0.001,
- thumb OR 13.43 [2.28; 78.99], p = 0.004,
- elbow OR 3.16 [1.33; 7.51], p = 0.009,
- forearm pronators OR 3.12 [0.97; 10.07], NS

At the final visit (between 13 and 21 weeks), no significant difference was observed between the XEOMIN and placebo group for these 4 groups of muscles.

In the open follow-up study (63.6 ± 17.6 weeks) MRZ 0410-2 which included 145/148 patients from study MRZ 0410-1, the Ashworth score was significantly improved ($p < 0.0001$) compared to baseline after the first 4 injections of XEOMIN in the five locations studied (wrist, finger, thumb, elbow, forearm pronators). This effect was maintained until the fifth injection for the wrist, the fingers and the forearm pronators ($p < 0.05$) and until the fourth for the thumb and the elbow ($p < 0.0001$) but was not maintained at the fifth injection (NS).

In a single-blind study comparing two different doses of XEOMIN (MRZ 0607) after 4 weeks of treatment, the percentage of responders (reduction of at least one point on the Disability Assessment Scale (DAS)) was 63% in the group on XEOMIN 20 U/ml and 52.4% in the group on XEOMIN 50 U/ml, a difference of 10.6%, 95% CI [-4.4; 24.9]. Since the lower limit of the confidence interval for the observed difference of -4.4 points was below the limit set in the protocol (-25%), the non-inferiority of XEOMIN 20 U/ml compared to XEOMIN 50 U/ml was accepted.

No study comparing the efficacy and tolerance of XEOMIN to those of other proprietary medicinal products containing Botulinum toxin type A (BOTOX, DYSPORT) is currently available.

There are no available data that would permit an assessment of the contribution of XEOMIN compared to or complementing the multidisciplinary approach involving in particular functional rehabilitation.

The most commonly observed adverse events were: pain and haematoma at the injection site, muscle weakness.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Spasticity is a incapacitating disability which can impair the quality of life and may have substantial social and familial repercussions.

This medicinal product is a symptomatic treatment.

It is a first-line drug treatment which must be used in addition to physiotherapy.

There are treatment alternatives.

Public health benefit:

Stroke is the leading cause of acquired disability in adults, the second most common cause of dementia and the third most common cause of mortality in France[4]. Few epidemiological data are available on the prevalence of post-stroke spasticity. It can be estimated that about 20% of patients who have had a stroke will develop spasticity[5].

The burden of spasticity is due to the functional disability and loss of independence that it causes. Its repercussions may also be not appreciable on a psychosocial, familial or even professional level. However, given the heterogeneity of the patients and the very variable degree of disability related to spasticity, the public health burden may be regarded as moderate.

Reducing the functional sequelae associated with stroke and improving the quality of life of persons with chronic diseases are public health needs that are already an established priority (Law of 9 August 2004 on public health policy – objective 72, Quality of Life Improvement Plan for Patients with Chronic Disorders, National Stroke Action Plan).

However, the data available are not sufficient to quantify the expected impact of Botulinum toxins on the improvement in functional incapacity and thus disability and on the improvement of the quality of life of spastic patients, even in the short term.

In view of the data from the study MRZ 0410-1 and in the absence of any study versus an active comparator, XEOMIN is not expected to have any additional impact compared to the other toxins already available.

The transferability of the results of studies to clinical practice is not assured: a single study covering a limited number of patients, initial comparability of the groups not assured, absence of information on the associated physiotherapy, no French patients, limited duration of the studies with a long-term treatment.

Moreover, as with other Botulinum toxins, it is expected to have an impact on the healthcare system because of the need to establish a multidisciplinary medical and paramedical organisation, for clinicians to be trained and gain experience and for personalised patient follow-up.

In view of all these factors, and consistent with what was proposed for other Botulinum toxins, there is not any expected public health benefit for XEOMIN in this indication.

The efficacy/adverse effects ratio is modest.

4 The prevention and management of strokes in France: summary of the report presented by Dr Elisabeth Fery-Lemonnier - June 2009.

5 D.K. Sommerfield et al. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. Stroke 2001; 35: 134-139.

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

4.2. Improvement in actual benefit (IAB)

The absence of comparative clinical data does not allow defining and assessing the advantage of XEOMIN compared to other types A Botulinum toxins. XEOMIN therefore does not provide any improvement in actual benefit (IAB V) compared to other treatments available for the post-stroke management of upper-limb spasticity with flexed wrist and clenched fist in adults.

4.3. Therapeutic use[6,7]

Muscle spasticity gives rise to pain and spasms and causes functional weakness of the upper or lower limbs. It may constitute disability or, in some patients, a means of compensating for a motor deficit.
The aetiologies of spasticity are disorders of the central nervous system (brain or spinal cord) of a vascular, traumatic, infectious or degenerative nature. Central neurological pain may appear in the same disorders. There is thus frequently a link between spasticity and central neuropathic pain.

The management of muscle spasticity depends on the clinical picture, the consequences and treatment options, depending on the diffuse or local nature and extent of the functional disability.

Physiotherapy is the first-line treatment.

Rehabilitation techniques that promote muscle stretching and can be combined with positioning by means of splints or plaster casts are to be preferred. These forms of transient immobilisation must be subject to careful monitoring, particularly cutaneous.

When a medicine is considered, it must always be combined with physiotherapy. In the case of localised spasticity, it is preferable to treat the muscles involved locally. The different techniques are:

Muscular injection of Botulinum toxin:
- Botulinum toxin type A is recommended[5] because there is established proof of its effect on the local reduction of spasticity after intramuscular injection (grade A); most of the results are from studies concerning adults who had had a stroke. It can be used as first-line treatment of focal or multifocal spasticity (professional consensus).
- Botulinum toxin B could have the same effects but there are not enough studies available to give reliable results. It is available on the market (NEUROBLOC) but does not have Marketing Authorisation in this indication.

Administration of baclofen or tinazidine:
Baclofen has demonstrated its action in the reduction of spasticity evaluated using the Ashworth muscle hypertonia scale.
Tizanidine, which is covered by a temporary usage authorisation (TUA), is recommended in the event of inefficacy, adverse effects or contraindications to baclofen (professional consensus).
These treatments are not recommended as first-line treatment after recent stroke because of their inadequate efficacy and adverse effects.

6 Fletcher D., “Spasticity and pain”, Evaluation and treatment of pain, SFAR 2003, p 125-133.
7 Drug treatments of spasticity. Good practice recommendations. AFSSAPS, June 2009.

In patients with a diffuse lesion, the administration of antispastic products such as dantrolene, or benzodiazepines (clonazepam, tetrazepam, off-label) can be proposed, despite low levels of evidence.

Nerve blocks (alcohol, phenol):
Alcohol and phenol have an action on spasticity assessed using the Ashworth score in that they reduce spasticity by chemical neurolysis (irreversible destruction of the nerve).
They are not the first-line local treatment except in certain cases of particularly diffuse and troublesome spasticity where they can sometimes be used to complement another local treatment (Botulinum toxin) (professional consensus).

The inefficacy of properly given treatment must give reason to consider surgical approaches. In extreme cases, central neurostimulation or destructive surgery (*DREZ lesion*, cordotomy) can be considered.

In all cases, the aim of treatment is to induce a localised reduction in muscle activity in order to improve motor function and reduce the disability and functional disturbance induced by spasticity.

Botulinum toxin (XEOMIN) must be administered by specialist doctors experienced in its use in these indications which represents an alternative to other type A Botulinum toxins. It is a reversible and adaptable local treatment.

4.3. Target population

The target population for XEOMIN in this extension of indication is made up of adult patients with upper-limb spasticity with flexed wrist and clenched fist following a stroke.

It can be estimated on the basis of the following factors:
- according to 2009 data from the programme for clinical information systems (PMSI), about 145,000 hospital admissions for stroke were observed,
- spasticity is said to be present in 16[8] to 19[9]% of post-stroke patients.

In view of these data, the target population of XEOMIN in this indication can be estimated at between 23,000 and 28,000 patients a year.

4.4. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the extension of indication and at the dosages in the Marketing Authorisation.

8 Spasticity in adults after stroke. CRMDM 2004.
9 Disa et al. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. Stroke 2004; 35: 134-9.