

ANNEX I

**LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL
PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS MARKETING
AUTHORISATION HOLDERS IN THE MEMBER STATES**

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>(Invented) Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>	<u>Content (concentration)</u>
Germany	Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany		Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	
Denmark	Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany		Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	
Sweden	Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany		Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	
Austria		Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	
Spain		Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	
Finland		Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	
France		Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	
Italy		Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	
Luxembourg		Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use	

Norway	Germany Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use
Poland	Germany Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use
Portugal	Germany Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use
UK	Germany Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt/Main Germany	Xeomin	100 LD ₅₀ units	Powder for solution for injection	For intramuscular use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF XEOMIN <(see Annex I)>

- Quality issues

From a quality point of view, Xeomin is highly purified and differs from the drug substance in Botox® and Dysport® in that it is free of complexing proteins (haemagglutinins).

No quality aspects were the subject of disagreement during the Mutual Recognition procedure.

- Efficacy issues

The clinical development program was composed by 5 studies provided in the following table:

Table 1: Table Listing of Clinical Studies

Trial Countries	Phase, Population and Design	Study Treatment	Primary Endpoint
COMPLETED STUDIES			
BTC-9901 Germany	Phase 1 14 healthy male volunteers Open-label, within treatment comparison	4 U Xeomin and Botox intramuscular	Change in maximal amplitude of CMAP
MRZ-0113 Germany	Phase 1b 32 healthy male volunteers Double-blind, within treatment comparison examining dose response profile, systemic diffusion and duration of effect	2, 4, 16 or 32 U of Xeomin and Botox intramuscular	Reduction in CMAP at Week 4 Follow up for 52 weeks
BTC-9801 Germany	Phase 2 dose ranging study 53 patients with rotational cervical dystonia Open-label, randomised, active-comparator trial	Xeomin: 10/20 U, 20/40 U, 30/60 U Botox 30/60 U intramuscular	Change in maximal amplitude of CMAP after 2 weeks
MRZ-0013 Europe and Israel	Phase 3 466 patients with cervical dystonia Double-blind, randomised, active-controlled (Botox), parallel trial	70-300 U Xeomin or Botox intramuscular	Change in TWSTRS – Severity score after 4 weeks
MRZ-0003 Europe and Israel	Phase 3 304 patients with blepharospasm Double-blind randomised, active-controlled (Botox), parallel trial	Up to 70 U of Xeomin or Botox intramuscular	Change in JRS sum score after 3 weeks

TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale
JRS: Jankovic Rating Scale
EDB: Extensor digitorum brevis
CMAP: Compound muscle action potential
U: Units

The submitted clinical trial programme consisted of:

- Two Phase I studies MRZ/BTC-9901 and MRZ/BTC-0113, of which the latter was performed after completion of the Phase III studies
- One Phase II study (MRZ/BTC-9801)
- Two Phase III studies (one study in each of the intended indication, spasmodic torticollis (MRZ/BTC-0013) and blepharospasm (MRZ/BTC-0003) respectively)

In addition, at present there are three ongoing clinical studies with Xeomin:

- In the upper limb spasticity study (MRZ 0410) 144 patients entered the second injection cycle, in which doses up to 400 U of Xeomin are administered.
- In the cervical dystonia study (MRZ 0408) in which doses up to 240 U of Xeomin are administered, 31 patients entered the second injection cycle.
- In the blepharospasmus study (MRZ 0433) one patient has entered the second injection cycle.

Posology

The applicant submitted three non-clinical, two Phase I, one Phase II and one Phase III studies to demonstrate that a safe posology has been established for Xeomin.

- Non-clinical data

In non-clinical studies, the pharmacological effect (i.e. degree of the paralytic activity, effect on motility, effect on paralysis over time, duration) of Xeomin was compared to Botox:

- The paralytic activity of Xeomin and Botox was assessed in the mouse regional paralysis test, after 3 repeated intramuscular injections at 6 and 13 week intervals up to a dose of 0.64 Lethal Dose Unit (LDU)/animal for Xeomin and Botox (approx. 32 LDU/kg).
- The influence of Xeomin and Botox on motility (static and active movements) was assessed within an acute intravenous toxicity study in mice up to 68 LDU/kg.
- The paralytic efficacy of Xeomin and Botox was analysed by electromyography (EMG) in vivo in male monkeys after a single intramuscular injection of 16 LDU/kg in the left gluteus medius muscle.

The nonclinical data clearly demonstrated that one unit of Xeomin is equipotent to one unit of Botox and a clear dose-response was shown in two species. Based on the results, it could be concluded that pharmacological effect of Xeomin and Botox are almost comparable in animals.

- Clinical data

Both Phase I studies showed equal doses of Xeomin to be as effective as Botox in the EMG measurements; it was clearly demonstrated that the paralytic effects of Xeomin and Botox increased with ascending doses and a comparable trend was seen in a Phase II study.

In Phase II dose finding trial, the efficacy in patients with rotational cervical dystonia at three doses (10, 20 and 30 U) of Xeomin was compared to the optimal dose of Botox (30 U).

The primary efficacy variable was the decrease from baseline of the most relevant (i.e. highest amplitude) surface electromyography (EMG) level in the dystonic sternocleidomastoid muscle during maximal voluntary activation 14 days post-injection. The study failed with respect to the determination of the optimal therapeutic dose of Xeomin in the treatment of spasmodic torticollis, as no statistically significant treatment differences (overall or pair-wise) were observed, but similar effectiveness of Xeomin and Botox in EMG measurements could be demonstrated. Nevertheless, the mean change of surface EMG level in the sternocleidomastoid muscle, which is to be regarded as an objective parameter, showed a clear dose-trend of Xeomin.

Considering the data from the non-clinical studies, the early Phase I study and its conclusions, and the Phase II study - although limited conclusions could be drawn from it, the dosage of Xeomin in both Phase III studies was based on the established dose of Botox. This approach is considered acceptable. During a Scientific Advice procedure in 2000, the EMEA did not require or recommend that further Phase II studies be conducted before the Phase III studies were performed.

The applicant presented efficacy data of Phase III study in spasmodic torticollis. This study showed the non-inferiority of Xeomin (70-300 U) compared to Botox (70-300 U). A similar dose-efficacy response relationship has been demonstrated for Xeomin and Botox after one injection in spasmodic torticollis Phase III study.

Taken altogether, the data from the non-clinical and clinical development program, which has been designed with support of Scientific Advice, provided sufficient evidence that a 1:1 dose ratio between Xeomin and Botox with respect to efficacy and safety can be concluded and the adoption of the dosage which has been established for Botox is adequately justified. Against this background a further extensive dose-ranging program would not have been justifiable from an ethical point of view.

- Safety data

The numbers of adverse events in Phase II study and in Phase III dystonia Study are submitted in the following Table:

Table 2: Summary of Adverse Events in Phase II Study (BTC 9801 and Phase III Cervical Dystonia Study (MRZ 0013)

	Phase II cervical dystonia trial (ITT) (BTC-9801)					Phase III cervical dystonia trial (ITT) (MRZ-0013)	
	Xeomin 10/20U	Xeomin 20/40U	Xeomin 30/60U	Botox 30/60U	Xeomin total	Botox	Xeomin
Total No. subjects	14	13	14	12	41	232	231
Subjects with AEs	5 (35.7%)	5 (38.5%)	2 (14.3%)	6 (50.0)	12 (29.3)	57 (24.6)	66 (28.1)

Due to the very low number in each group, results of this Phase II study were not considered to be useful from a safety point a view. It should be noted that some adverse events have only been reported in patients who received Xeomin, such as dysphagia (reported in one patient in each of the Xeomin groups versus no patients in the Botox group). In addition, two adverse events have been assessed as related to study medication, versus none in the Botox group. The two related adverse events were reported in the same patient who received 30/60 U of Xeomin (one injection site pain and one dysphagia).

The fact that the Phase III studies were performed in patients pretreated with Botox is adequately addressed in the SPC, which now states that ‘there is limited experience in treatment-naïve patients’.

Lack of data on repeated administration and the need for data on immunogenicity

- Non-clinical data

Two non-clinical studies, LPT10929 and LPT12444 with repeated high dose administration of Xeomin (25 LDU/animal in LPT10929 and 16-40LDU/animal in LPT12444) at very short injection intervals were performed in rabbits:

- In LPT10929, in study week 12, two weeks after the last administration, Botulinum neurotoxin type A neutralising antibodies were found in 4 of 8 surviving rabbits treated with Botox, but in none of the 10 surviving rabbits treated with Xeomin.

- In LPT12444, in week 36, three weeks after the final injection, the ELISA test (indicating the presence of antibodies against Botulinum neurotoxin type A) revealed that seven of the 20 rabbits treated with Botox showed a positive response and four of these rabbits displayed BoNT/A neutralising activity in the hemidiaphragm assay (HDA indicating if antibodies are neutralising or non-neutralising). In contrast, one animal treated with Xeomin was tested positively in the ELISA test, but no neutralising activity was detected in the HDA.

In the non-clinical study, Xeomin was not more or less immunogenic than Botox even at dose levels clearly exceeding the recommended human dose.

- Clinical data

Botox and Xeomin are different drug substances in terms of clostridial protein content, although both contain the same 150 kDa neurotoxin, which is the actual active substance. Botox has a protein content of 5 ng/100U, i.e. the 150 kDa neurotoxin and non-effective complexing proteins, and quickly dissociates into the neurotoxin and the complexing proteins after administration. Xeomin has a protein content of only 0,6 ng/100U as it only consists of the 150 kDa neurotoxin, free from complexing proteins. By reason of these facts it is implausible, that injection of Xeomin would lead to more frequent secondary therapeutic failures than Botox.

Xeomin has been developed with the aim of reducing the risk of formation of neutralising antibodies, which may lead to secondary therapy failure. Publications of clinical studies have been mentioned

(Jankovic et al, 2003¹, 2006², Barnes et al, 2005³) to support the hypothesis that the amount of antibodies is correlated to the amount of clostridial protein load and thus, that there might be a lower risk for patients treated with Xeomin to develop secondary non-response.

In 2003, Jankovic compared 130 patients treated for cervical dystonia with original Botox (25ng protein/100 U before 1998), 42 of whom were exposed only to the original Botox and 119 treated with the current Botox (5ng protein/100 U since 1998). Blocking antibodies were detected in 4 of 42 (9.5%) patients treated only with original Botox and in none of the patients treated with only the current Botox, despite a higher mean dose of current Botox per visit than original Botox. These findings must be interpreted cautiously because all patients were not systematically tested for Botulinum toxin antibodies.

The immunological reactions on Xeomin were specifically investigated in the Phase III study MRZ-0013 in patients with cervical dystonia. Data of changes in TWSTRS-Severity score in patients with hemidiaphragm assay (HDA) positive group between control visit (3 weeks after one injection) and final visit (12 weeks after one injection) were submitted. These data were divided into 3 subgroups: patients with HDA negative, patients with positive antibodies < 5 mU/mL and patients with positive antibodies > 5 mU/mL.

Of the Xeomin patients with a negative mouse hemidiaphragm assay (HDA) result at baseline, indicating that no neutralising antibodies are present, 2 individuals had a positive result (<5 mU/mL) at the final visit. Of the Botox patients 4 individuals with a negative result at baseline had a positive result (<5 mU/mL in 3 patients, >5 mU/mL in 1 patient) at the final visit. In addition, the HDA titer increased from <5 mU/mL to >5 mU/mL in 2 patients in each treatment group. In both treatment groups, 4 patients with a positive HDA result at baseline had a negative result at the final visit.

In the Phase III study MRZ-0003 in patients with blepharospasm, no patient in both treatment groups had a HDA antibody titer higher than 1 mU/l at baseline or at final visit.

The informational value of the Phase III studies concerning immunogenicity is limited, as the patients were pretreated with Botox, and Xeomin was administered only once. Therefore, no valid conclusions can be drawn from the resulting data with respect to immunogenicity of Xeomin compared to Botox. However, there is no indication of a higher antigenic potential of Xeomin compared to Botox.

At present there are three ongoing clinical studies with Xeomin (all of which have a placebo-controlled single injection main period and subsequent extension periods, in which only Xeomin is administered). In each of the ongoing studies, data are still blinded, but no secondary therapy failures due to antibody development have been reported up to now.

In the upper limb spasticity study (MRZ 0410) 144 patients entered the 2nd injection cycle, in which doses up to 400 U of Xeomin are administered. One hundred and ten patients are in the 3rd and 13 patients in the 4th injection cycle. HDA tests are performed at baseline and repeatedly during the course of the study and the results which are, amongst others, available for 107 patients after the 2nd injection cycle and for 73 patients four weeks after 3rd injection did not show any neutralising antibodies.

In the cervical dystonia study (MRZ 0408) in which doses up to 240 U of Xeomin are administered, 63 patients received the 2nd injection, 27 patients received the 3rd, and 6 patients received the 4th injection, respectively. Up to now the FIA (Fluorescence Immuno Assay) screening test revealed no trend of a development of antibodies after Xeomin injection. The HDA tests of the available samples were still in analysis, when the applicant's response was circulated. Meanwhile the respective results

¹ Jankovic J, Vuong KD, Ahsan J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. *Neurology* 2003; 60(7): 1186-1188.

² Jankovic J, Hunter C, Dolimbek BZ, Dolimbek GS, Adler CH, Brashear A, et al. Clinicoimmunologic aspects of botulinum toxin type B treatment of cervical dystonia. *Neurology* 2006; 67(12): 2233-2235.

³ Barnes MP, Best D, Kidd L, Roberts B, Stark S, Weeks P, et al. The use of Botulinum toxin type-B in the treatment of patients who have become unresponsive to Botulinum toxin type-A -- initial experiences. *Eur J Neurol* 2005; 12(12): 947-955.

are available, showing one positive test result at baseline and before 3rd injection and two positive results four weeks after 1st injection and before 2nd injection. However, as one of the two positive results four weeks after 1st injection and before 2nd injection was found in a patient pretreated with Botox and the study is still blinded, no conclusions concerning immunogenicity of Xeomin can be drawn from these results.

The applicant is requested to submit the results of all scheduled HDA tests of the upper limb spasticity study (MRZ 0410) and the cervical dystonia study (MRZ 0408) after unblinding of the respective studies.

In the blepharospasmus study (MRZ 0433) 6 patients received the 2nd injection.

Thus, up to now no case of secondary therapy failure can be derived from the ongoing studies, in which Xeomin (or placebo) has been used repetitively in a total of 213 patients, even though Xeomin doses are partially very high (which is usually a risk factor of antibody formation).

The applicant has committed to perform a post-marketing surveillance study, in which immunogenicity of Xeomin will be further investigated after repeated administration (up to 6 injection sessions). The study proposed is an open, single arm study in which 74 patients with cervical dystonia (naïve and pre-treated) are planned.

Lastly, the proposed SPC for Xeomin does not claim a potentially lower risk of development of antibodies with the product: "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 neurotoxin type A complex. In cases of non-response, alternative therapies should be taken into consideration."

Safety profile

- Overall Comparison of Adverse Events in Phase I – III Studies

A total of five clinical trials (BTC-9901, MRZ-0113, BTC-9801, MRZ-0013, MRZ-0003) have been completed to provide data on the safety and efficacy of Xeomin. Overall, safety data from 908 participants have been included in these trials, 466 subjects were treated with Xeomin and 442 subjects were treated with Botox.

Of the 908 participants, 239 thereof experienced adverse events (AEs). An almost identical percentage of patients in both treatment groups reported AEs (26.6% in the Xeomin group and 26.0% in the Botox group). The most common AEs (i.e. with an incidence of $\geq 1\%$) were dysphagia, ptosis, back and skeletal pain and muscle weakness, the majority of them assessed as mild or moderate. The only severe case of dysphagia occurred in the Botox group.

The applicant has submitted the total number of adverse events with no distinction between adverse events related or not related. The difference of the total number of adverse events related or not related between Xeomin and Botox was not statistically significant.

- Phase III Cervical Dystonia Study (MRZ 0013)

In this trial, 65 out of 231 patients (28.1%) treated with Xeomin reported a total of 110 adverse events. For Botox, 57 out of 232 patients (24.6%) reported a total of 90 adverse events. Most of the adverse events were of mild or moderate severity in both groups. The most frequently reported adverse event was dysphagia (Xeomin 10.8%; Botox 8.2%; $p=0.29$). One case with severe dysphagia was reported in the Botox group.

- Phase III Blepharospasm Study

In this trial, 40 out of 148 patients (27.0%) treated with Xeomin reported a total of 57 adverse events. For Botox, 45 out of 152 patients (29.6%) reported a total of 62 adverse events. All adverse events were of mild or moderate severity except one case of treatment-related ptosis in the Xeomin and one case of unrelated myocardial infarction in the Botox group. The most frequently reported adverse event was ptosis (Xeomin 6.1%; Botox 4.6%).

However, in clinical trials the **related adverse events** were numerically more frequent in the Xeomin group compared to the Botox group.

	Phase III study in cervical dystonia (MRZ 60201-0013)		Phase III study in blepharospasm , (MRZ 60201-0003)	
	XEOMIN (n=231)	BOTOX (n=232)	XEOMIN (n=148)	BOTOX (n=155)
Patients with related adverse effects	38 (16.5%)	27 (11.6%)	18 (12.1 %)	13 (8.38 %)
95 % CI of differences between related adverse effect proportions (Xeomin versus Botox)	(-1.5% ; +11.3%)		(-3.2% ; +11%)	

Thus, related adverse effects occurred more frequently in the Xeomin group compared to Botox.

The rate of serious adverse events (SAEs) in all studies was 2.1% with Xeomin and 2.7% with Botox. All of the SAEs were assessed as unrelated to treatment.

One death (colon carcinoma), assessed as unrelated to study treatment (Botox), was reported during the Phase II cervical dystonia study.

Three patients discontinued the studies prematurely due to adverse events considered as unrelated to study drug.

Post-marketing experience revealed no different or new safety signals for Xeomin compared to other Botulinum toxin containing medicinal products.

1.3 RECOMMENDATION

The applicant has committed to perform a post-marketing study, in which immunogenicity of Xeomin is further investigated after repeated administration (up to 6 injection sessions).

The applicant is requested to submit the results of all scheduled HDA tests of the upper limb spasticity study (MRZ 0410) and the cervical dystonia study (MRZ 0408) after unblinding of the respective studies.

Overall, the safety data shows that the prevalence of adverse events (AEs) was nearly identical in the Xeomin and in the Botox group (26.6% vs. 26%, respectively).

The most frequent at least possibly related AE was **dysphagia** (5.2% for Xeomin vs. 3.4% for Botox in the pooled sample and 10% for Xeomin vs. 8.2% in the cervical dystonia Phase III study, respectively). No statistical differences were found between both treatment groups. Of note, the only severe case of dysphagia occurred in a Botox treated patient.

The second most frequent (at least possibly related) AE **ptosis** was reported in a comparable degree (1.9% for Xeomin vs. 1.8% for Botox in the pooled sample and 6.1% for Xeomin vs. 4.6% for Botox in the blepharospasm Phase III study) and occurred in BPS patients only. Treatment-related muscular weakness was observed in 1.1% of all patients randomised to Xeomin vs. 0.2% of all Botox patients, whereas the Phase Ib study MRZ-0113 showed no difference in the diffusion of both preparations in adjacent muscles.

The incidence of Serious Adverse Events was low in all studies, with a similar frequency in both treatment groups. No drug-related SAE was reported, there were no withdrawals due to adverse events.

In addition to the list of follow-up measures discussed and requested by the CMDh, the CHMP requested the following follow-up measures to be submitted to the National Competent Authorities and to be assessed under the co-ordination of the RMS:

- To perform a post-marketing study to confirm the safety and efficacy of Xeomin after repeated injections (up to 6 injection sessions).
- To submit the results of a pharmacodynamic study in which “spread” of neurotoxin is quantified in comparison to two other Botox preparations.
- To submit the results of all scheduled HDA tests of the upper limb spasticity study (MRZ 0410) and the cervical dystonia study (MRZ 0408) after unblinding of the respective studies.
- To submit a Risk Management Plan, according to the current guideline, including:
 - Detailed strategies for educating physicians including appropriate injection techniques, dosing and lack of interchangeability between products as well as programmes for continued and improved monitoring of spread reactions in clinical use and in clinical trials.
 - Information on usage patterns and on types of prescribers/users of Xeomin in order to identify if and at what type of clinics off-label cosmetic use is taking place, especially in the EU.
 - Steps to be taken to ensure that patients are adequately informed of the safety issues associated with these products, e.g. adequate labelling and patient brochures. Specifically this information should include advice to seek immediate medical help in the event of swallowing, speech or respiratory difficulties arise.
 - Specifically include toxin spread events in their sentinel list of events for active monitoring.
 - Evaluation of the spread reactions, specifically as part of future studies.
 - Commitment to alert the National Competent Authorities if there is a significant change in reporting rate.

GROUND FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the potential risk to public health concerning the need for data in repeated administration and data on immunogenicity for Xeomin
- the posology of Xeomin
- the safety profile of Xeomin in the two Phase III clinical trials

based on the documentation submitted by the Marketing Authorisation Holder and the scientific discussion within the Committee,

the CHMP has recommended the granting of the Marketing Authorisation for which the Summary of Product Characteristics, Labelling and Package Leaflet are set out in Annex III for Xeomin.

ANNEX III

**SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xeomin 100 LD₅₀ units powder for solution for injection
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 100 LD₅₀ units* of Clostridium Botulinum neurotoxin type A (150 kD), free of complexing proteins.

* One unit corresponds to the median lethal dose (LD₅₀) when the reconstituted product is injected intraperitoneally into mice under defined conditions.

Due to differences in the LD₅₀ assay, these units are specific to Xeomin and are not interchangeable with other Botulinum toxin preparations.

Excipient(s):

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection

White powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xeomin is indicated for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults.

4.2 Posology and method of administration

Unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.

Xeomin may only be used by physicians with suitable qualifications and proven experience in the application of Botulinum toxin and in the use of the necessary equipment, e.g. EMG (electromyography).

Reconstituted Xeomin is intended for intramuscular injection.

The optimum dosage and number of injection sites in the treated muscle should be determined by the physician individually for each patient. A titration of the dose should be performed.

For instructions on reconstitution / dilution of the vials, see section 6.6. After reconstitution, Xeomin should be used for only one injection session and for only one patient.

A decrease or increase in the Xeomin dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less pressure sensation and the less spread of Botulinum neurotoxin type A in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

Blepharospasm

After reconstitution, the Xeomin solution is injected using a suitable sterile needle (e.g. 27-30 gauge/0.30-0.40 mm). Electromyographic guidance is not necessary. An injection volume of approximately 0.05 to 0.1 ml is recommended.

Xeomin is injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision.

The initial recommended dose is 1.25-2.5 U (0.05-0.1 ml volume) at each site. The initial dose should not exceed 25 U per eye. In the management of blepharospasm, total dosing should not exceed 100 U every 12 weeks.

Injections near the levator palpebrae superioris should be avoided to reduce the occurrence of ptosis. Diplopia may develop as a result of Botulinum neurotoxin type A diffusion into the inferior oblique. Avoiding medial injections into the lower lid may reduce this adverse reaction.

The median first onset of effect is observed within four days after injection. The effect of each treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter. The treatment can be repeated if required.

At repeat treatment sessions, the dose may be increased up to two-fold if the response to the initial treatment is considered insufficient – usually defined as an effect that does not last longer than two months. However, there appears to be no additional benefit obtainable from injecting more than 5.0 U per site. Normally, no additional benefit is conferred by treating more frequently than every three months.

Spasmodic torticollis

In the management of spasmodic torticollis, Xeomin dosing must be tailored to the individual patient, based on the patient's head and neck position, location of possible pain, muscle hypertrophy, patient's body weight, and response to the injection. A suitable sterile needle (e.g. 25-30 gauge/0.30-0.50 mm) is used for injections into superficial muscles, and an e.g. 22 gauge/0.70 mm needle may be used for injections into deeper musculature. An injection volume of approximately 0.1 to 0.5 ml is recommended.

In the management of spasmodic torticollis, Xeomin is usually injected into the sternocleidomastoid, levator scapulae, scalenus, splenius capitis, and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment. If difficulties arise isolating single muscles, injections should be performed using electromyographic guidance. The muscle mass and the degree of hypertrophy or atrophy are factors to be taken into consideration when selecting the appropriate dose.

In practice, the maximum total dose is usually not more than 200 U. Doses of up to 300 U may be given. No more than 50 U should be given at any one injection site.

Multiple injection sites permit Xeomin more uniform coverage of the innervated areas of the dystonic muscle and are especially useful in larger muscles. The optimum number of injection sites is dependent upon the size of the muscle to be chemically denervated.

The sternocleidomastoid should not be injected bilaterally as there is an increased risk of adverse reactions (in particular dysphagia) when bilateral injections or doses in excess of 100 U are administered into this muscle.

The median first onset of effect is observed within seven days after injection. The effect of each treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter. The period between each treatment session should be at least 10 weeks.

All indications

If no treatment effect occurs within a month after the initial injection, the following measures should be taken:

- clinical verification of the neurotoxin effect on the injected muscle: e.g. an electromyographic investigation in a specialised facility
- analysis of the reason for non-response, e.g. poor isolation of the muscles intended to be injected, too low dose, poor injection technique, fixed contracture, too weak antagonist, 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 failure to respond, 2) EMG-guidance, 3) the recommended minimum interval between the initial and repeat treatment is not exceeded

The 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.

4.3 Contraindications

Hypersensitivity to the active substance Botulinum neurotoxin type A or to any of the excipients.

Generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome).

Presence of infection at the proposed injection site.

4.4 Special warnings and precautions for use

Side effects related to spread of Botulinum toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.

Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with underlying neurological disorders including swallowing difficulties are at increased risk of these side effects. The Botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

An anaphylactic reaction may occur rarely after injection of Botulinum neurotoxin type A (see section 4.8). Adrenaline and other medical aids for treating anaphylaxis should be available.

Prior to administering Xeomin the physician must make himself familiar with the patient's anatomy and any alterations to the anatomy due to prior surgical procedures. Extra caution is

required when injecting at sites close to sensitive structures such as the carotid artery and lung apices.

There is limited experience in treatment-naïve patients and long-term treatment.

Xeomin should be used with caution:

- if bleeding disorders of any type occur
- in patients receiving anticoagulant therapy
- in patients suffering from amyotrophic lateral sclerosis or other diseases which result in peripheral neuromuscular dysfunction
- in targeted muscles which display pronounced weakness or atrophy.

The recommended single doses of Xeomin should not be exceeded and the intervals between injections should not be shortened.

The clinical effects of Botulinum neurotoxin type A can increase or decrease by repeated injections. The possible reasons are different techniques of reconstitution, the chosen injection intervals, the injected muscles and marginally varying toxin activity resulting from the biological testing procedure employed or secondary non-response.

Too frequent dosing of Botulinum toxin may result in antibody formation which may lead to resistance to treatment (see section 4.2).

Previously akinetic or sedentary patients should be reminded to gradually resume activities following the injection of Xeomin.

Xeomin contains albumin, a derivative of human blood. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include careful selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. There are no reports of viral transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

Blepharospasm

Because of the anticholinergic effect of Botulinum neurotoxin type A, Xeomin should be used with caution in patients at risk of developing an angle closure glaucoma.

In order to prevent ectropion, injections into the lower lid area should be avoided, and vigorous treatment of any epithelial defect is necessary. This may require protective drops, ointments, soft bandage contact lenses, or closure of the eye by patching or similar means.

Reduced blinking following Xeomin injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve disorders (facial nerve). Careful testing of corneal sensation should be performed in patients with previous eye operations.

Ecchymosis easily occurs in the soft tissues of the eyelid. Immediate gentle pressure at the injection site can limit that risk.

Spasmodic torticollis

Patients should be informed that injections of Xeomin for the management of spasmodic torticollis may cause mild to severe dysphagia with the risk of aspiration and dyspnoea. Medical intervention may be necessary (e.g. in the form of a gastric feeding tube) (see also section 4.8). Dysphagia can last for up to two to three weeks after injection, but a duration of up to five months has been reported in one case. Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who require bilateral injections into the sternocleidomastoid muscles are at greater risk. The occurrence of dysphagia is attributable to the spread of the pharmacological effect of Xeomin as the result of the neurotoxin spread into the oesophageal musculature.

4.5 Interaction with other medicinal products and other forms of interaction

Theoretically, the effect of Botulinum neurotoxin may be potentiated by aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission e.g. tubocurarine-type muscle relaxants.

Therefore the concomitant use of Xeomin with aminoglycosides or spectinomycin requires special care. Peripheral muscle relaxants should be used with caution, if necessary reducing the starting dose of relaxant, or using an intermediate-acting substance such as vecuronium or atracurium rather than substances with longer lasting effects.

4-Aminochinolines may reduce the effect of Xeomin.

4.6 Pregnancy and lactation

There are no adequate data from the use of Botulinum neurotoxin type A in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Therefore, Xeomin should not be used during pregnancy unless clearly necessary and unless the potential benefit justifies the risk.

It is not known whether Botulinum neurotoxin type A is excreted into the breast milk. Therefore, the use of Xeomin during lactation cannot be recommended.

4.7 Effects on ability to drive and use machines

Xeomin has minor or moderate influence on the ability to drive and use machines.

Due to the nature of the diseases being treated, the ability to drive and to operate machines can be reduced. Due to the latency of onset, some of the therapeutic and/or adverse effects of Xeomin may also interfere with the ability to drive and operate machinery. Consequently affected persons should avoid these tasks until their faculties are fully recovered.

4.8 Undesirable effects

Undesirable effects may occur from misplaced injections of Botulinum neurotoxin type A temporarily paralysing nearby muscle groups. Large doses may cause paralysis in muscles distant to the injection site. Usually, undesirable effects are observed within the first week after treatment and are temporary in nature. They may be restricted to the area around the injection site (e.g. local pain, tenderness at the injection site, and injection site haemorrhage).

Frequency by different indications

Based on clinical experience information on the frequency of adverse reactions for the individual indications is given below. The frequency categories are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$).

Blepharospasm

The following adverse reactions were reported with Xeomin:

Nervous system disorders

Uncommon: paraesthesia, headache

Eye disorders

Common: ptosis, dry eyes

Uncommon: conjunctivitis

Gastrointestinal disorders

Uncommon: dry mouth

Skin and subcutaneous tissue disorders

Uncommon: skin rash

Musculoskeletal and connective tissue disorders

Uncommon: muscle weakness

Injury, poisoning and procedural complications

Uncommon: inflicted injury

Additionally, the following undesirable effects and accordingly their frequencies are known for the comparative compound containing conventional Botulinum toxin type A complex used in clinical trials with Xeomin. It is possible that these undesirable effects may also occur with Xeomin.

Nervous system disorders

Uncommon: dizziness, facial paralysis

Eye disorders

Common: superficial punctate keratitis, lagophthalmos, eye irritation, photophobia, lacrimation

Uncommon: keratitis, ectropion, diplopia, entropion, visual disturbance, blurred vision

Rare: swelling of eyelid

Very rare: angle closure glaucoma, corneal ulceration

Skin and subcutaneous tissue disorders

Uncommon: dermatitis

Musculoskeletal and connective tissue disorders

Uncommon: facial muscle weakness

General disorders and administration site conditions

Uncommon: tiredness

Spasmodic torticollis

The following adverse reactions were reported with Xeomin:

Nervous system disorders

Uncommon: headache, tremor

Eye disorders

Uncommon: eye pain

Respiratory, thoracic and mediastinal disorders

Uncommon: dysphonia

Gastrointestinal disorders

Common: dysphagia

Uncommon: diarrhoea, dry mouth, vomiting, colitis

Skin and subcutaneous tissue disorders

Uncommon: skin rash, erythema, pruritus, sweating increased

Musculoskeletal and connective tissue disorders

Common: muscle weakness, back pain

Uncommon: skeletal pain, myalgia

General disorders and administration site conditions

Uncommon: asthenia, injection site inflammation, injection site tenderness

Additionally, the following undesirable effects and accordingly their frequencies are known for the comparative compound containing conventional Botulinum toxin type A complex used in clinical trials with Xeomin. It is possible that these undesirable effects may also occur with Xeomin.

Nervous system disorders

Common: dizziness, numbness, drowsiness

Eye disorders

Uncommon: diplopia, ptosis

Respiratory, thoracic and mediastinal disorders

Common: rhinitis, upper respiratory tract infection

Uncommon: dyspnoea, voice alteration

Gastrointestinal disorders

Common: nausea, oral dryness

Skin and subcutaneous tissue disorders

Common: skin sores

Musculoskeletal and connective tissue disorders

Common: stiffness, hypertonia

General disorders and administration site conditions

Very common: pain, local weakness

Common: generalised weakness, flu like symptoms, malaise

Uncommon: fever

The management of spasmodic torticollis may cause dysphagia with varying degrees of severity with the potential for aspiration which may require medical intervention. Dysphagia may persist

for two to three weeks after injection, but has been reported in one case to last five months. Dysphagia appears to be dose-dependent. In clinical trials with Botulinum toxin type A complex it was reported that dysphagia occurs less frequently with total doses below 200 U per treatment session.

General

The following additional information is based on publications on conventional preparations containing the Botulinum toxin type A complex.

Side effects related to spread of toxin distant from the site of administration have been reported very rarely (exaggerated muscle weakness, dysphagia, aspiration pneumonitis with fatal outcome in some cases) (see section 4.4).

Dysphagia has been reported following injection to sites other than the cervical musculature.

There have been rare reports of undesirable effects related to cardiovascular system, such as arrhythmia and myocardial infarction, some with fatal outcomes. It remains unclear whether these deaths were induced by conventional preparations containing the Botulinum toxin type A complex or caused by pre-existing cardiovascular disease.

A case of peripheral neuropathy has been reported in a male after receiving four sets of injections of a conventional preparation containing the Botulinum toxin type A complex (for neck and back spasm, and severe pain) over an 11 week period.

A female patient developed brachial plexopathy two days after injection of a conventional preparation containing the Botulinum toxin type A complex for the treatment of cervical dystonia, with recovery after five months.

Erythema multiforme, urticaria, psoriasis-like rash, pruritus, and allergic reactions have been described with the use of conventional preparations containing the Botulinum toxin type A complex, but their causal relationship remains unclear.

Following injection of conventional Botulinum toxin type A complex, EMG showed increased jitter in some distant muscles which was not associated with muscle weakness or other types of electrophysiological abnormalities.

4.9 Overdose

Symptoms of overdose:

Increased doses of Botulinum neurotoxin type A may result in pronounced neuromuscular paralysis distant from the injection site. Symptoms of overdose are not immediately apparent post-injection and may include general weakness, ptosis, diplopia, swallowing and speech difficulties or paralysis of the respiratory muscles resulting in an aspiration pneumonia.

Measures in cases of overdose:

In case of an overdose the patient must be monitored medically for several days. If signs of intoxication appear, hospitalisation with general supportive measures is necessary. Intubation and assisted ventilation will become necessary until improvement if paralysis of the respiratory muscles occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxant, peripherally acting agent, ATC code: M03AX01

Botulinum neurotoxin type A blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine. The nerve terminals of the neuromuscular junction no longer respond to nerve impulses, and secretion of the neurotransmitter is prevented (chemical denervation). Recovery of impulse transmission is re-established by the formation of new nerve terminals and motor endplates.

The mechanism of action by which Botulinum neurotoxin type A exerts its effects on cholinergic nerve terminals can be described by a three-step sequential process which includes the following steps:

- a) binding to the cholinergic nerve terminals
- b) entry or internalisation into the nerve terminal and
- c) inhibition of acetylcholine release by intracellular poisoning within the nerve terminal.

The heavy chain of the Botulinum neurotoxin type A binds with an exceptionally high selectivity and affinity to receptors only found on cholinergic terminals. After internalisation of the neurotoxin the light chain cleaves very specifically a target protein (SNAP 25) that is essential for the release of acetylcholine.

Recovery after injection normally takes place within 3-4 months as nerve terminals sprout and reconnect with the endplate.

5.2 Pharmacokinetic properties

a) General characteristics of the active substance:

Classic kinetic and distribution studies cannot be conducted with Botulinum neurotoxin type A because the active substance is applied in such small quantities (picograms per injection), and because it binds so rapidly and irreversibly to cholinergic nerve terminals.

Native Botulinum toxin is a high molecular weight complex, which, in addition to the neurotoxin (150 kD) contains other non-toxic proteins, like haemagglutinins and non-haemagglutinins. In contrast to conventional preparations containing the Botulinum toxin type A complex, Xeomin contains pure (150 kD) neurotoxin since it is free of complexing proteins.

Like many other proteins of its size, Botulinum neurotoxin type A has been shown to undergo retrograde axonal transport after intramuscular injection. Retrograde transsynaptic passage of active Botulinum neurotoxin type A into the central nervous system however has not been found.

Receptor-bound Botulinum neurotoxin type A is endocytosed into the nerve terminal prior to reaching its target (SNAP 25) and will eventually be degraded intracellularly. Free circulating Botulinum neurotoxin type A molecules which have not bound to presynaptic cholinergic nerve terminal receptors will be phagocytosed or pinocytosed and degraded like any other free circulating protein.

b) Distribution of the active substance in patients:

Human pharmacokinetic studies with Xeomin have not been performed for the reasons detailed above.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of cardiovascular safety pharmacology.

The findings made in repeat-dose toxicity studies conducted with Xeomin were mainly related to its pharmacodynamic action.

No evidence of local intolerance was noted. Reproductive toxicity studies with Xeomin, performed in rabbits, did not show adverse effects on male or female fertility nor direct effects on embryo-foetal development. However, the administration of Xeomin at dose levels exhibiting clear maternal toxicity at weekly to biweekly intervals increased the number of abortions in a prenatal toxicity study in rabbits. A continuous systemic exposure of the dams during the (unknown) sensitive phase of the organogenesis as a pre-requisite for the induction of teratogenic effects cannot necessarily be assumed.

No genotoxicity, carcinogenicity and pre- and postnatal development studies have been conducted with Xeomin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Sucrose

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 3 years

Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C. From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Unopened vial: Do not store above 25°C

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (type 1 glass) with rubber stopper (bromobutyl rubber) and tamper-proof seal (aluminium) in pack sizes of 1 (single unit pack), 2, 3 or 6 vials (multi-packs). A clinical pack is also available with 6 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Xeomin is reconstituted prior to use with sterile unpreserved sodium chloride 9 mg/ml (0.9%) solution for injection. Reconstitution and dilution should be performed with good practice, particularly with respect to asepsis.

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of solvent (see dilution table) is drawn up into a syringe. The exposed portion of the rubber stopper of the vial is cleaned with alcohol (70%) prior to insertion of the needle. The solvent must be injected gently into the vial. The vial must be discarded, if the vacuum does not pull the solvent into the vial. Reconstituted Xeomin is a clear colourless solution free of particulate matter.

Xeomin should not be used if the reconstituted solution (prepared as above) has a cloudy appearance or contains floccular or particulate matter.

The recommended dilutions are indicated in the following table:

Solvent added (sodium chloride 9 mg/ml (0.9%) solution for injection)	Resulting dose in units per 0.1 ml
0.5 ml	20.0 U
1.0 ml	10.0 U
2.0 ml	5.0 U
4.0 ml	2.5 U
8.0 ml	1.25 U

Any solution for injection that has been stored for more than 24 hours as well as any unused solution for injection should be discarded.

For safe disposal, unused vials should be reconstituted with a small amount of water and then autoclaved. Any used vials, syringes, and spillage etc. should be autoclaved and any residual Xeomin inactivated using diluted sodium hydroxide solution (0.1 N NaOH).

7. **MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

8. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

[To be completed nationally]

10. **DATE OF REVISION OF THE TEXT**

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON FOR SINGLE UNIT PACK (1 VIAL)****1. NAME OF THE MEDICINAL PRODUCT**

Xeomin100 LD₅₀ units powder for solution for injection
Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 100 LD₅₀ units of Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

3. LIST OF EXCIPIENTS

Human albumin, sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHODS AND ROUTE(S) OF ADMINISTRATION

For intramuscular use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S); IF NECESSARY**8. EXPIRY DATE**

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

After reconstitution: the product may be stored for a maximum of 24 hours at 2°C to 8°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

For safe disposal, unused vials should be reconstituted with a small amount of water then sterilised under high pressure. Any used vials, syringes, and spillage etc. should be autoclaved and any residual Xeomin inactivated using diluted sodium hydroxide solution (0.1 N NaOH).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

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12. MARKETING AUTHORISATION NUMBER(S)
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[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 VIAL WHEN THIS IS PART/COMPONENT OF A MULTIPACK WITH 2, 3, 6 VIALS

1. NAME OF THE MEDICINAL PRODUCT

Xeomin100 LD₅₀ units powder for solution for injection
Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 100 LD₅₀ units of Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

3. LIST OF EXCIPIENTS

Human albumin, sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHODS AND ROUTE(S) OF ADMINISTRATION

For intramuscular use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S); IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

After reconstitution: the product may be stored for a maximum of 24 hours at 2°C to 8°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

For safe disposal, unused vials should be reconstituted with a small amount of water then sterilised under high pressure. Any used vials, syringes, and spillage etc. should be autoclaved and any residual Xeomin inactivated using diluted sodium hydroxide solution (0.1 N NaOH).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

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12. MARKETING AUTHORISATION NUMBER(S)
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[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 VIAL WHEN THIS IS PART/COMPONENT OF A CLINICAL PACK WITH 6 VIALS

1. NAME OF THE MEDICINAL PRODUCT

Xeomin100 LD₅₀ units powder for solution for injection
Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 100 LD₅₀ units of Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

3. LIST OF EXCIPIENTS

Human albumin, sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHODS AND ROUTE(S) OF ADMINISTRATION

For intramuscular use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S); IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

After reconstitution: the product may be stored for a maximum of 24 hours at 2°C to 8°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

For safe disposal, unused vials should be reconstituted with a small amount of water then sterilised under high pressure. Any used vials, syringes, and spillage etc. should be autoclaved and any residual Xeomin inactivated using diluted sodium hydroxide solution (0.1 N NaOH).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

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12. MARKETING AUTHORISATION NUMBER(S)
--

[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON FOR MULTI PACK WITH 2, 3, 6 VIALS****1. NAME OF THE MEDICINAL PRODUCT**

Xeomin100 LD₅₀ units powder for solution for injection
Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 100 LD₅₀ units of Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

3. LIST OF EXCIPIENTS

Human albumin, sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
2 vials
3 vials
6 vials

5. METHODS AND ROUTE(S) OF ADMINISTRATION

For intramuscular use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S); IF NECESSARY**8. EXPIRY DATE**

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

After reconstitution: the product may be stored for a maximum of 24 hours at 2°C to 8°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

For safe disposal, unused vials should be reconstituted with a small amount of water then sterilised under high pressure. Any used vials, syringes, and spillage etc. should be autoclaved and any residual Xeomin inactivated using diluted sodium hydroxide solution (0.1 N NaOH).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

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12. MARKETING AUTHORISATION NUMBER(S)
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[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON FOR CLINICAL PACK WITH 6 VIALS****1. NAME OF THE MEDICINAL PRODUCT**

Xeomin100 LD₅₀ units powder for solution for injection
Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 100 LD₅₀ units of Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

3. LIST OF EXCIPIENTS

Human albumin, sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
6 vials
Clinical pack. For hospital use only

5. METHODS AND ROUTE(S) OF ADMINISTRATION

For intramuscular use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S); IF NECESSARY**8. EXPIRY DATE**

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

After reconstitution: the product may be stored for a maximum of 24 hours at 2°C to 8°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

For safe disposal, unused vials should be reconstituted with a small amount of water then sterilised under high pressure. Any used vials, syringes, and spillage etc. should be autoclaved and any residual Xeomin inactivated using diluted sodium hydroxide solution (0.1 N NaOH).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)
--

[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xeomin100 LD₅₀ units powder for solution for injection
Clostridium Botulinum neurotoxin type A (150kD), free of complexing proteins

For intramuscular use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: MM/JJJJ

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 LD₅₀ units

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Xeomin100 LD₅₀ units powder for solution for injection

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

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Xeomin is and what it is used for
2. Before you use Xeomin
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1. WHAT XEOMIN IS AND WHAT IT IS USED FOR

Xeomin is a medicine that relaxes the muscles.

Xeomin is used for the treatment of the following conditions in adults:

- eyelid spasm (blepharospasm)
- twisted neck (spasmodic torticollis)

2. BEFORE YOU USE XEOMIN

Do not use Xeomin

- if you are allergic (hypersensitive) to Botulinum neurotoxin type A or any of the other ingredients of Xeomin (see section 6 “Further information”)
- if you suffer from generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome)
- if an infection is present at the injection site.

Take special care with Xeomin

Tell your doctor:

- if you suffer from any type of bleeding disorders
- if you receive substances that prevent the blood from clotting (anticoagulant therapy)
- if you suffer from pronounced weakness or decreased muscle volume in the muscle where you will receive the injection
- if you suffer from a disease called amyotrophic lateral sclerosis. This disease leads to a wasting of muscle tissue.

- if you suffer from any disease that disturbs the interaction between nerves and skeletal muscles (peripheral neuromuscular dysfunction)
- if you have or have had swallowing difficulties

In cases of repeated injections with Xeomin, the therapeutic effect of the product may vary. The possible reasons for an increase or decrease are:

- different techniques of preparation of the product by your doctor
- different treatment intervals
- injections into another muscle
- marginally varying effectiveness of the active substance of Xeomin
- non-response/therapy failure during the course of treatment.

If you have been inactive for a long period of time, any activity should be started gradually after the Xeomin injection.

If you develop swallowing difficulties, speech or breathing disorders, please contact medical emergency services or ask your relatives to do so (see section 4).

The use of Xeomin in children and adolescents has not yet been investigated and is therefore not recommended.

Eyelid spasm (blepharospasm)

Please inform your doctor prior to any treatment, if you:

- have had an eye surgery. Your doctor will then take additional precautions.
- are at risk of developing a disease called angle closure glaucoma. This disease can cause the inner eye pressure to rise and may lead to a damaging of your optic nerve. Your doctor will know if you are at risk.

During treatment, small punctuated bleedings may occur in the soft tissues of the eyelid. Your doctor can limit these by immediately applying gentle pressure at the injection site.

After you receive a Xeomin injection into your eye muscle your blinking rate may be reduced. This can lead to an overlong exposure of the transparent front part of the eye (cornea). This exposure may lead to a damaging of the surface and an inflammation (corneal ulceration). This can occur more often if you suffer from disorders of your facial nerves.

Twisted neck (spasmodic torticollis)

After the injection you may develop mild to severe swallowing difficulties. This may lead to problems with breathing and you may have a higher risk of inhaling foreign substances or fluids. Foreign substances in your lungs may lead to an inflammation or infection (pneumonia). Your doctor will give you special medical treatment if needed (e.g. in the form of artificial nutrition).

Swallowing difficulties can last for up to two to three weeks after injection, for one patient a duration of up to five months is known.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Theoretically, the effect of Xeomin may be increased by:

- aminoglycoside antibiotics
- medicinal products that interfere with the transfer of an impulse from a nerve to a muscle, e.g. tubocurarine-type muscle relaxants that weaken the muscles.

Therefore, the concomitant use of Xeomin with aminoglycosides or spectinomycin requires special care. This is also relevant for medicinal products that weaken the muscle. Your doctor may reduce the starting dose of relaxant, or use an intermediate-action substance rather than substances with longer lasting effects.

Theoretically, the effect of Xeomin may be reduced by:

- certain anti-malaria / anti-rheumatic medicines (4-Aminochinolines).

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant, Xeomin should not be used, unless your doctor could decide whether there is a clear necessity and whether the potential benefit justifies the risk.

It is not known whether the active substance of Xeomin is excreted into the breast milk. Therefore, the use of Xeomin in breast-feeding women is not recommended.

Driving and using machines

Due to the nature of your disease being treated, the ability to drive and to operate machines can be reduced. Some of the therapeutic and/or side effects of Xeomin may also interfere with the ability to drive and operate machinery. Consequently you should avoid driving and operating machinery until your faculties are fully recovered.

3. HOW TO USE XEOMIN

Xeomin may only be used by health care professionals experienced in the application of Botulinum toxin.

Dissolved Xeomin is intended for injections into the muscle.

The optimum dosage and number of injection sites in the treated muscle will be chosen by your doctor individually for you. The results of initial treatment with Xeomin should be evaluated and may lead to dose adjustment until the desired therapeutic effect is achieved.

If you have the impression that the effect of Xeomin is too strong or too weak, let your doctor know. In cases where no therapeutic effect is apparent, alternative therapies should be taken into consideration.

Your body may develop antibodies after you received Botulinum toxin type A preparations. Antibodies may reduce the therapeutic effectiveness of the product.

Eyelid spasm (blepharospasm)

Usually, the first onset of effect is observed within four days after injection. The effect of each treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter. The treatment can be repeated if required.

Normally, no additional benefit is conferred by treating more frequently than every three months.

Twisted neck (spasmodic torticollis)

Usually, the first onset of effect is observed within seven days after injection. The effect of each treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter. The period between each treatment session should be at least 10 weeks.

If more Xeomin is used than should be

Symptoms of overdose

Symptoms of overdose are not apparent immediately after the injection and may be general weakness, drooping eyelid, double vision, swallowing and speech difficulties, and pneumonia.

Measures in cases of overdose

In case you feel symptoms of overdose please seek medical emergency services immediately or ask your relatives to do so, and have yourself admitted to hospital. Medical supervision for up to several days and assisted ventilation may be necessary.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xeomin can cause side effects, although not everybody gets them.

Side effects may occur from misplaced injections of Xeomin temporarily paralysing nearby muscle groups. Large doses may cause paralysis in muscles distant to the injection site. Usually, side effects are observed within the first week after treatment and are temporary in nature. They may be restricted to the area around the injection site (e.g. local pain, tenderness at the injection site, and injection site haemorrhage).

If you develop swallowing difficulties, speech or breathing disorders, please contact medical emergency services immediately or ask your relatives to do so.

As with any medicine, an allergic reaction may occur with Xeomin. An allergic reaction can cause any of the following symptoms:

- difficulty in breathing
- swelling of the hands, feet, ankles, face, lips, mouth or throat.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you suffer from any of these symptoms.

The following side effect probabilities and allocated frequencies are used for the categorisation of side effects:

<i>very common</i>	more than 1 per 10 treated people
<i>common</i>	less than 1 per 10, but more than 1 per 100 treated people
<i>uncommon</i>	less than 1 per 100, but more than 1 per 1,000 treated people
<i>rare</i>	less than 1 per 1,000, but more than 1 per 10,000 treated people
<i>very rare</i>	less than 1 per 10,000 treated people, incl. isolated cases

Eyelid spasm (blepharospasm)

The following side effects were reported with Xeomin:

Common: drooping eyelid (ptosis), dry eyes

Uncommon: muscle weakness, pins and needles (paraesthesia), headache, inflammation of the conjunctiva (conjunctivitis), dry mouth, skin rash, inflicted injury

Additionally, the following side effects are known for the comparative compound containing conventional Botulinum toxin type A complex used in the clinical trials with Xeomin. It is possible that these side effects may also occur with Xeomin:

Common: special form of inflammation of the cornea (superficial punctate keratitis), inability to close eye (lagophthalmos), eye irritation, fear of light (photophobia), tearing (lacrimation)

Uncommon: facial paralysis, facial muscle weakness, inflammation of the cornea (keratitis), everted margin of the lid (ectropion), double vision (diplopia), inverted margin of the lid (entropion), visual disturbance, blurred vision, dizziness, inflammatory skin reaction (dermatitis), tiredness

Rare: swelling of eyelid

Very rare: disease of the vision nerve, usually associated with an increased pressure inside the eye (angle closure glaucoma), corneal ulceration

Twisted neck (spasmodic torticollis)

The following side effects were reported with Xeomin:

Common: swallowing difficulties (dysphagia), muscle weakness, back pain

Uncommon: speech disorders (dysphonia), weakness (asthenia), muscle pain (myalgia), headache, shaking (tremor), eye pain, diarrhoea, dry mouth, vomiting, inflammation of the colon (colitis), skin rash, skin redness (erythema), itching (pruritus), sweating increased, skeletal pain, injection site inflammation, injection site tenderness

Additionally, the following side effects are known for the comparative compound containing conventional Botulinum toxin type A complex used in the clinical trials with Xeomin. It is possible that these side effects may also occur with Xeomin:

Very common: pain, local weakness

Common: generalised weakness, flu like symptoms, malaise, dizziness, numbness, sleepiness (drowsiness), nasal inflammation (rhinitis), upper respiratory tract infection, nausea, oral dryness, skin sores, stiffness, increased muscle tone (hypertonia)

Uncommon: breathing difficulties (dyspnoea), double vision (diplopia), drooping eyelid (ptosis), voice alteration, fever

The treatment of twisted neck may cause swallowing difficulties with varying degrees of severity. These may lead to breathing in foreign materials, which may require medical intervention. Swallowing difficulties may persist for two to three weeks after injection, but has been reported in one case to last five months. Swallowing difficulties appear to be dose-dependent. In clinical trials with Botulinum toxin type A complex, it was reported that swallowing difficulties occur less frequently with low doses.

General

The following additional information is based on publications on conventional preparations containing the Botulinum toxin type A complex.

Side effects related to spread of toxin distant from the site of administration have been reported very rarely (excessive muscle weakness, swallowing difficulties, lung infection or inflammation due to the inhalation of foreign substances (aspiration pneumonitis) with fatal outcome in some cases).

There are rare reports on side effects related to the cardiovascular system, such as irregular heartbeat (arrhythmia) and heart attack, some of them with fatal outcome. It remains unclear whether these deaths were induced by conventional preparations containing the Botulinum toxin type A complex or caused by a pre-existing cardiovascular disease.

Rare reports of severe allergic (anaphylactic) reactions after injection of a conventional preparation containing the Botulinum toxin type A complex have been received.

A case of peripheral neuropathy has been reported in a male after receiving four sets of injections of a conventional preparation containing the Botulinum toxin type A complex (for neck and back spasm, and severe pain) over an 11 week period.

A female patient developed a nerve lesion affecting the arm (brachial plexopathy) two days after injection of a conventional preparation containing the Botulinum toxin type A complex for the treatment of twisted neck, with recovery after five months.

Various forms of skin eruptions (erythema multiforme, urticaria, psoriasis-like rash), itching, and allergic reactions have been described with the use of conventional preparations containing the Botulinum toxin type A complex, but their causal relationship remains unclear.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE XEOMIN

Keep out of the reach and sight of children.

Do not use Xeomin after the expiry date which is stated on the carton and vial label after “EXP”. The expiry date refers to the last day of that month.

Unopened vial: Do not store above 25°C

Reconstituted solution: Store in a refrigerator (2 - 8°C)

Your doctor will reconstitute the medicine with physiological saline before use. This reconstituted solution may be stored for up to 24 hours at 2 to 8 °C. Nevertheless the product should be used immediately.

Your doctor should not use Xeomin if the vial reconstituted according to the instructions has a cloudy appearance or contains e.g. floccular or particulate matter.

6. FURTHER INFORMATION

What Xeomin contains

- The active substance is Clostridium Botulinum neurotoxin type A (150 kD), free of complexing proteins

1 vial contains 100 LD₅₀ units Clostridium Botulinum neurotoxin type A (150 kD), free of complexing proteins. One LD₅₀ unit corresponds to the median lethal dose (LD₅₀) when the reconstituted product is injected intraperitoneally into mice under defined conditions. Due to differences in the LD₅₀ assay, these units are specific to Xeomin and are not applicable to other Botulinum toxin preparations.
- The other ingredients are: human albumin, sucrose

What Xeomin looks like and contents of the pack

Xeomin is presented as a powder for solution for injection. The powder is white.
When dissolved Xeomin is a clear and colourless solution which is free of particulate matter.

Pack sizes of 1 (single unit pack), 2, 3 or 6 vials (multi-packs).
Not all pack sizes may be marketed.

Marketing Authorisation Holder

[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

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Manufacturer

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Phone: +49-69/15 03-1
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The following information is intended for medical or healthcare professionals only:

A decrease or increase in the Xeomin dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less pressure sensation and less spread of Botulinum neurotoxin type A in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

Xeomin is reconstituted prior to use with sterile unpreserved sodium chloride 9 mg/ml (0.9%) solution for injection.

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of solvent (see dilution table) is drawn up into a syringe. The exposed portion of the rubber stopper of the vial is cleaned with alcohol (70%) prior to insertion of the needle. The solvent must be injected gently into the vial. The vial must be discarded, if the vacuum does not pull the solvent into the vial. Reconstituted Xeomin is a clear colourless solution free of particulate matter.

The recommended dilutions are indicated in the following table:

Solvent added (sodium chloride 9 mg/ml (0.9%) solution for injection)	Resulting dose in units per 0.1 ml
0.5 ml	20.0 U
1.0 ml	10.0 U
2.0 ml	5.0 U
4.0 ml	2.5 U

8.0 ml	1.25 U
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Special precautions for disposal

Any solution for injection that has been stored for more than 24 hours as well as any unused solution for injection should be discarded.

For safe disposal, any unused vials should be dissolved with a small amount of water and then sterilised under high pressure (autoclaved). Any used vials, syringes, and spillage etc. should be sterilised under high pressure and any residual Xeomin inactivated using diluted sodium hydroxide solution (0.1 N NaOH).