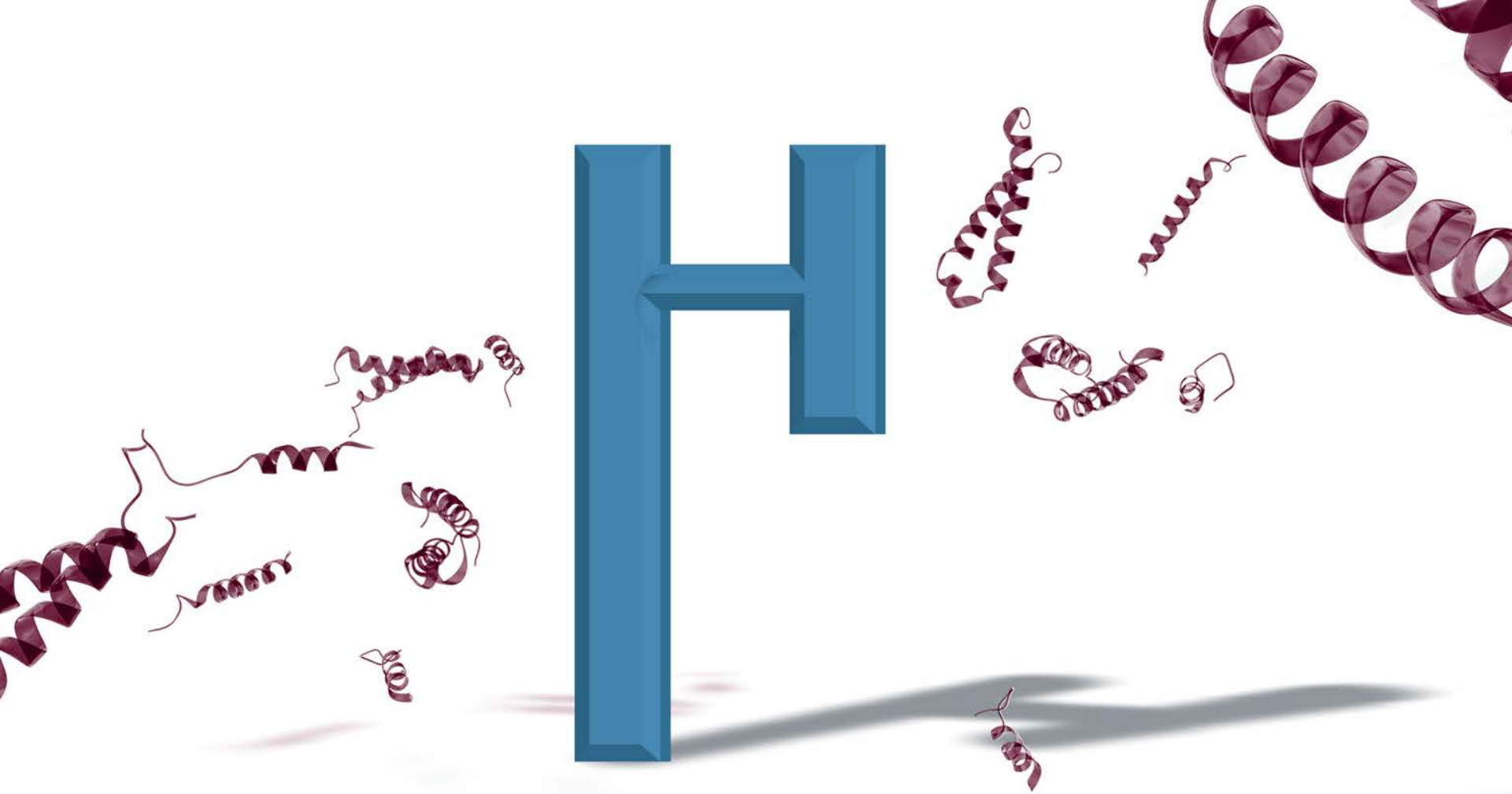

XEOMIN in Dystonia* and Spasticity** Treatment Information for Health Care Professionals

08 May 2016

* XEOMIN is indicated for the symptomatic treatment of blepharospasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults
** XEOMIN is indicated for the symptomatic treatment of post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist in adults
For full details please refer to the most currently approved SmPC

Introduction

Introduction

- With this document, <Merz Pharmaceuticals> provides information to health care professionals as a key element of the Risk Management Plan (RMP) for XEOMIN according to the PhVWP Report on Clostridium Botulinum toxin products, Doc.Ref.: EMEA/CHMP/PhVWP/129856/2007
- The goal of this information is to minimise the potential risks associated with the use of XEOMIN
- To achieve this goal, this material provides information on the reduction of the risk of adverse events – such as dysphagia - due to unintended toxin spread or inappropriate injection technique as detailed in the table of contents

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Appropriate Injection Technique

Injection Technique – General for All Indications

- XEOMIN may only be administered by physicians/health care professionals with suitable qualifications and requisite experience in the application of Botulinum toxin
- Use 25-30 gauge needles for injection into superficial muscles
- For deeper musculature it may be necessary to use larger needles (e.g. 22 gauge, 75 mm length)
- The optimum dosage and number of injection sites in the treated muscle(s) should be determined by the physician individually for each patient

Injection technique – Blepharospasm

- XEOMIN is injected into the medial and lateral orbicularis oculi muscle of the upper lid and the lateral orbicularis oculi muscle of the lower lid. Additional sites in the brow area, the lateral orbicularis oculi muscle and in the upper facial area may also be injected if spasms here interfere with vision
- Sterile 27-30 gauge needles are suitable for the injection
- An injection volume of approximately 0.05 to 0.1 ml per injection site is recommended
- Injections near the levator palpebrae superioris should be avoided to reduce the occurrence of ptosis
- Medial injections into the lower lid should be avoided as to reduce the risk of diplopia due to toxin spread into the inferior oblique muscle
- Ecchymosis easily occurs in the soft tissues of the eyelid. Immediate gentle pressure at the injection site can limit that risk
- 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

Injection technique – Spasmodic Torticollis

- XEOMIN is 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
- 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
- A suitable sterile needle (e.g. 25-30 gauge / 0.30-0.50 mm) is used for injections into superficial muscles, and a larger needle (e.g. 22 gauge / 0.70 mm) may be used for injections into deeper musculature

Injection technique – Spasmodic Torticollis

- An injection volume of approximately 0.1 to 0.5 ml per injection site is recommended
- 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 units are administered into this muscle

Injection technique – Post Stroke Spasticity of the Upper Limb

- In superficial muscles, a sterile needle (e.g. 26 gauge, 37 mm) is suitable for administration; for deeper musculature, a larger sterile needle (e.g. 22 gauge, 75 mm) is suitable
- In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance. Multiple injection sites may allow XEOMIN to have more uniform contact with the innervation areas of the muscle and are especially useful when larger muscles are injected.
- For the muscles injected in the pivotal trial, please see the respective table in the chapter “Appropriate Dose and Injection Interval”

Appropriate Dose and Injection Interval

Dosing & Injection Interval - Blepharospasm

- The initial recommended dose is 1.25-2.5 units per injection site. The initial dose should not exceed 25 units per eye. Total dosing should not exceed 100 units every 12 weeks
- At repeat treatment sessions, the dose may be increased up to two-fold if the response to the initial treatment is considered insufficient
- There appears to be no additional benefit obtainable from injecting more than 5.0 units per site
- The median time to first onset of effect is observed within four days after injection
- The effect of a XEOMIN treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter. The treatment can be repeated if required.
- Treatment intervals should be determined based on the actual clinical need of the individual patient.

Dosing & Injection Interval - SpasmodicTorticollis

- 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
- No more than 200 units should be injected for the first course of therapy with adjustments made in the subsequent courses depending on the response. A total dose of 300 units at any one sitting should not be exceeded
- No more than 50 units should be administered at any one injection site
- Median first onset of effect is within seven days after injection
- The muscle mass and the degree of hypertrophy or atrophy are factors to be taken into consideration when selecting the appropriate dose
- The effect of treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter
- Treatment intervals of less than 10 weeks are not recommended. Treatment intervals should be determined based on the actual clinical need of the individual patient

Dosing & Injection Interval - Post Stroke Spasticity of the Upper Limb

- 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
- The maximum total recommended dose is up to 400 units per treatment session
- Patients reported the onset of action 4 days after treatment. The maximum effect as an improvement of muscle tone was perceived within 4 weeks
- In general, the treatment effect lasted 12 weeks. Repeated treatment should generally be no more frequent than every 12 weeks

Dosing & Injection Interval - Post Stroke Spasticity of the Upper Limb

- Recommended initial doses and doses for repeated treatment:

Clinical pattern	Muscle	Mean initial dose/Units	Repeated treatment dose range/Units	Injection sites per muscle
Flexed wrist	*Flexor carpi radialis*	50	25-100	1-2
	Flexor carpi ulnaris	40	20-100	1-2
Clenched fist	*Flexor digitorum superficialis*	40	40-100	2
	Flexor digitorum profundus	40	40-100	2
Flexed elbow	*Brachioradialis*	60	25-100	1-3
	Biceps	80	75-200	1-4
	Brachialis	50	25-100	1-2
Pronated forearm	*Pronator quadratus*	25	10-50	1
	Pronator teres	40	25-75	1-2
Thumb-in-palm	*Flexor pollicis longus*	20	10-50	1
	Adductor pollicis	10	5-30	1
	Flexor pollicis brevis/Opponens pollicis	10	5-30	1

Consistent observation of risk factors for toxin spread reactions and caution in the presence of risk factors

Risk Factors for Toxin Spread Reactions - General for All Indications

- Consideration of special warnings
  - Undesirable effects may occur from misplaced injections of Botulinum toxin type A that temporarily paralyse nearby muscle groups. Large doses may cause paralysis in muscles distant from the injection site
  - There have been reports of undesirable effects that might be related to the spread of Botulinum toxin type A to sites far from the injection site. Some of these can be life threatening and there have been reports of death, which in some cases was associated with dysphagia, pneumonia and/or significant debility
  - Dysphagia has also been reported following injection to sites other than the cervical musculature

Risk Factors for Toxin Spread Reactions - General for All Indications

- Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with neuromuscular disorders may be at increased risk of exaggerated muscle weakness. The Botulinum toxin type A 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 occur

Risk Factors for Toxin Spread Reactions - General for All Indications

- Consideration of precautions for use in patients
  - suffering from amyotrophic lateral sclerosis (ALS)
  - with other diseases which result in peripheral neuromuscular dysfunction
  - In targeted muscles which display pronounced weakness or atrophy
  - with bleeding disorders of any type
  - receiving anticoagulant therapy or taking other substances that could have an anticoagulant effect
  - with altered anatomy due to prior surgical procedures
  - when injecting at sites close to sensitive structures (e.g. carotid artery, lung apices, oesophagus)
- Care should be taken to ensure that XEOMIN is not injected into a blood vessel
- The recommended single doses of XEOMIN should not be exceeded

Risk Factors for Toxin Spread Reactions - Blepharospasm

- Very common reported undesirable effects with XEOMIN in blepharospasm are eyelid ptosis and dry eyes
- The full list of undesirable effects is listed in the Summary of Product Characteristics (SmPC, see Appendix)
- Because of the anticholinergic effect of Botulinum toxin type A, XEOMIN should be used with caution in patients at risk of developing a narrow angle 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

SmPC: Summary of Product Characteristics

Risk Factors for Toxin Spread Reactions - Spasmodic Torticollis

- Very common reported undesirable effect with XEOMIN in Spasmodic Torticollis is dysphagia
- The full list of undesirable effects is listed in the Summary of product characteristics (SmPC, see Appendix)
- 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
- 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)
- Limiting the dose injected into the sternocleidomastoid muscle to less than 100 units 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 of developing dysphagia

SmPC: Summary of Product Characteristics

Use of the correct bioequivalent dose when switching from one Botulinum toxin product to another

Bioequivalent dose

- Due to unit differences in the potency assay, unit doses for XEOMIN are not interchangeable with those for other preparations of Botulinum toxin

- Non-inferiority of XEOMIN efficacy as compared to a comparator product containing the conventional Botulinum toxin type A complex onabotulinumtoxinA (900 kD) was shown in two comparative single-dosing Phase III studies, one in patients with blepharospasm (study MRZ 60201-0003, n=300) and one in patients with cervical dystonia (study MRZ 60201-0013, n=463). Study results also suggest that XEOMIN and this comparator product have a similar efficacy and safety profile in patients with blepharospasm or cervical dystonia when used in a dosing conversion ratio of 1:1

Discussion with the patient on benefit/risk and awareness of the educational material for patients

Discussion with the patient

- 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).
- Dysphagia has also been reported following injection to sites other than the cervical musculature.
- Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur
- Consider and discuss undesirable effects, especially if the history of the patient points to an increased risk for these (see chapter „Risk factors for toxin spread reactions“)

- Hand over the Patient Information Sheet (see Appendix)

Legal Information / Appendix

Legal information

- Number of version: 4.0 (Date: 2015-05-08)
- Copyright notice: This material is intended to be used to inform health care professionals about the safe use of XEOMIN and potential risks. Any unauthorized copying or distribution is prohibited
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Appendix – XEOMIN SmPC & Patient Information Sheet

- Attached you can find
  - The XEOMIN Summary of Product Characteristics (SmPC)
  - The Patient Information Sheet