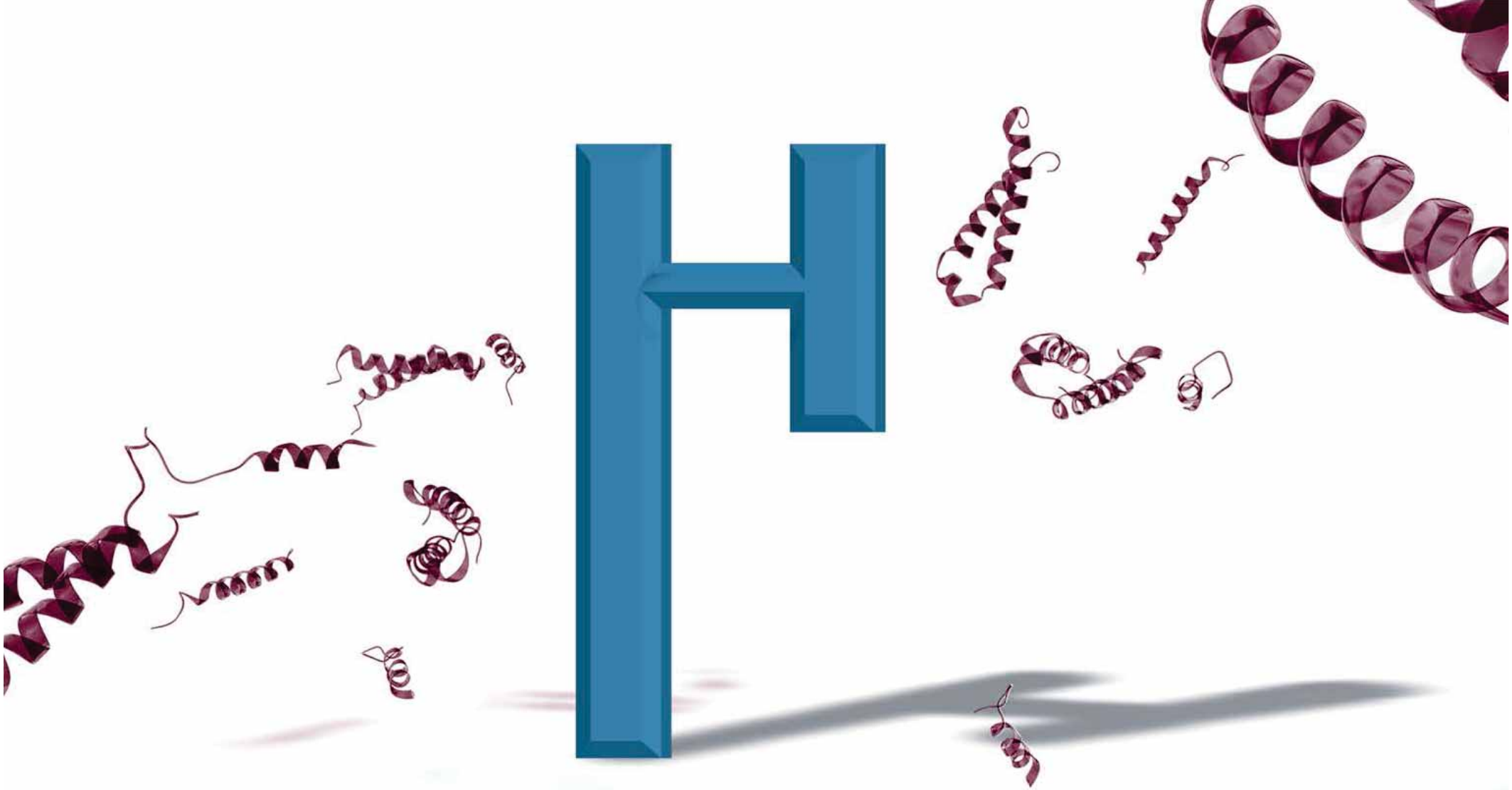

XEOMIN in Dystonia* and Spasticity** Treatment Information for Health Care Professionals

11 April 2014

* 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 PowerPoint presentation, Merz Pharmaceuticals provides information to health care professionals as a key element of the Risk Management Plan (RMP)* for XEOMIN
- 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

* According to the PhVWP Report on Clostridium botulinum toxin products, Doc.Ref.: EMEA/CHMP/PhVWP/129856/2007

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* According to the PhVWP Report on Clostridium botulinum toxin products, Doc.Ref.: EMEA/CHMP/PhVWP/129856/2007

Appropriate Injection Technique

Injection Technique – General for All Indications

- XEOMIN may only be administered by physicians with suitable qualifications and proven experience in the application of Botulinum toxin and in the use of the necessary equipment, e.g. electromyography (EMG)
- Use 25-30 gauge needles for injection into superficial muscles
- With deeper musculature it may be necessary to use larger needles (e.g. 22 gauge)
- The optimum number of injection sites in the treated muscle should be determined by the physician individually for each patient

Injection technique – Blepharospasm

- 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
- Sterile 27-30 gauge needles are suitable for the injection
- An injection volume of approximately 0.05 to 0.1 mL 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
- The risk of ecchymosis can be limited by immediate gentle pressure at the injection site

Injection technique – 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
- 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 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 per injection site is recommended

Injection technique – Post Stroke Spasticity of the Upper Limb

- In superficial muscles, a sterile 26 gauge, 37 mm length needle is suitable for administration; for deeper musculature, a sterile 22 gauge, 75 mm length needle is suitable
- Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. Multiple injection sites may allow XEOMIN to have more uniform contact with the innervation areas of the muscle and 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 recommended initial dose is 1.25-2.5 units at each site. The total initial dose should not exceed 25 units per eye. Total dosing should not exceed 100 units per treatment session
- 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 2 months
- There appears to be no additional benefit obtainable from injecting more than 5.0 units per site
- Median time to first onset of effect is usually within four days after injection

- The effect of each treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter

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
- The total dose should not exceed 200 U per treatment session. Doses of up to 300 units may be given
- No more than 50 units should be given at any single injection site
- 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
- Median time to first onset of effect is usually 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

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
- Median time to first onset of effect is usually within four days after injection

- In general, the treatment effect lasts 12 weeks. Reinjections should not be performed within intervals of less than12 weeks

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

- Dosing should be tailored to the individual patient's need. Recommended dose ranges for XEOMIN in upper limb post-stroke spasticity are given below:

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 neurotoxin type A that temporarily paralyse nearby muscle groups
  - Undesirable effects related to spread of Botulinum toxin distant from the injection site of administration have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility. Patients with a history of dysphagia and aspiration should be treated with extreme caution
  - Botulinum toxin should only be used under specialist supervision in patients with underlying neurological disorders, including swallowing difficulties, as the risk of exaggerated muscle weakness is increased. 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
  - Dysphagia has also been reported following injection to sites other than the cervical musculature

Risk Factors for Toxin Spread Reactions - General for All Indications

- Consideration of precautions for use in patients
  - In patients with amyotrophic lateral sclerosis (ALS)
  - In patients with other diseases which result in peripheral neuromuscular dysfunction
  - In targeted muscles which display pronounced weakness or atrophy
  - In patients with bleeding disorders
  - In patients receiving anticoagulant therapy or taking other substances in anticoagulant doses
  - With altered anatomy due to prior surgical procedures
  - When injecting at sites close to sensitive structures (e.g. carotid artery, lung apices, oesophagus)

Risk Factors for Toxin Spread Reactions - Blepharospasm

- Common reported undesirable effects for XEOMIN in blepharospasm are ptosis and dry eyes
- The full list of undesirable effects is listed in the SmPC (see Appendix)
- Injections into the lower lid area should be avoided to prevent ectropion
- Consider precautions for use
  - Caution in patients at risk of developing a narrow angle glaucoma
  - Vigorous treatment of any epithelial defect with protective eyedrops, ointments, soft bandage contact lenses, or closure of the eye by patching or similar means
  - Testing of corneal sensation in patients with previous eye operations

SmPC: Summary of Product Characteristics

Risk Factors for Toxin Spread Reactions - Spasmodic Torticollis

- Common reported undesirable effects for XEOMIN in Spasmodic Torticollis are dysphagia, muscle weakness, and back pain
- The full list of undesirable effects is listed in the 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
- Consider precautions for use
  - Limiting the dose injected into the sternocleidomastoid to less than 100 units may decrease the occurrence of dysphagia
  - Patients with smaller neck muscle mass are at greater risk for developing dysphagia and should be treated with greater care
  - Patients who require bilateral injections into the sternocleidomastoid muscles are at greater risk for 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 LD_{50} assay, XEOMIN units are specific to XEOMIN. Therefore unit doses recommended 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 in blepharospasm and cervical dystonia, 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 arise
- 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: 3.1 (Date: 2014-04-11)
- Copyright notice: This material is intended to be used to inform physicians 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 SmPC
  - The Patient Information Sheet