XEOMIN (Botulinum neurotoxin Type A)
Important Risk Minimisation Information for Healthcare Professionals

11 April 2014
Licensed Indications for Xeomin

XEOMIN is indicated for:

- Symptomatic treatment of blepharospasm in adults
- Cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults
- Symptomatic treatment of post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist in adults

For further prescribing information please refer to the most currently approved SPC via www.medicines.ie or www.hpra.ie
Introduction

- With this PowerPoint presentation, Merz Pharma UK Ltd. provides information to health care professionals as a key element of the Risk Management Plan (RMP)* for XEOMIN
- This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks and therefore you are advised to view the presentation carefully before prescribing/administering the product.
- The aim of this material is to minimise the identified risks of dysphagia and the local or systemic spread of the toxin, associated with this product.

* According to the PhVWP Report on Clostridium botulinum toxin products, Doc.Ref.: EMEA/CHMP/PhVWP/129856/2007
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- Appropriate injection technique
- Appropriate dose and injection intervals
- Consistent observation of risk factors for toxin spread reactions and caution in the presence of risk factors
- The use of the correct bioequivalent dose when switching from one botulinum toxin product to another
- A thorough discussion with the patients on benefit/risk and awareness of the educational material for patients
- Legal Information / Appendix

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XEOMIN (Botulinum neurotoxin Type A)

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)
- 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 potential spread of the Botulinum neurotoxin type A in the injected muscle. This could be of benefit in reducing effects on nearby muscles when small muscle groups are being injected.
- 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.
- 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.
- 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”
XEOMIN (Botulinum neurotoxin Type A)

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 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 – 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.
- Normally, no additional benefit is conferred by treating more frequently than every 3 months.
Dosing & Injection Interval - 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.
- Normally, in practice, the total dose does 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.
- 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 than 12 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:

<table>
<thead>
<tr>
<th>Clinical pattern</th>
<th>Muscle</th>
<th>Mean initial dose/Units</th>
<th>Repeated treatment dose range/Units</th>
<th>Injection sites per muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexed wrist</td>
<td>Flexor carpi radialis</td>
<td>50</td>
<td>25-100</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>Flexor carpi ulnaris</td>
<td>40</td>
<td>20-100</td>
<td>1-2</td>
</tr>
<tr>
<td>Clenched fist</td>
<td>Flexor digitorum superficialis</td>
<td>40</td>
<td>40-100</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Flexor digitorum profundus</td>
<td>40</td>
<td>40-100</td>
<td>2</td>
</tr>
<tr>
<td>Flexed elbow</td>
<td>Brachioradialis</td>
<td>60</td>
<td>25-100</td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td>Biceps</td>
<td>80</td>
<td>75-200</td>
<td>1-4</td>
</tr>
<tr>
<td></td>
<td>Brachialis</td>
<td>50</td>
<td>25-100</td>
<td>1-2</td>
</tr>
<tr>
<td>Pronated forearm</td>
<td>Pronator quadratus</td>
<td>25</td>
<td>10-50</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pronator teres</td>
<td>40</td>
<td>25-75</td>
<td>1-2</td>
</tr>
<tr>
<td>Thumb-in-palm</td>
<td>Flexor pollicis longus</td>
<td>20</td>
<td>10-50</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Adductor pollicis</td>
<td>10</td>
<td>5-30</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Flexor pollicis brevis/Opponens pollicis</td>
<td>10</td>
<td>5-30</td>
<td>1</td>
</tr>
</tbody>
</table>
XEOMIN (Botulinum neurotoxin Type A)

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 treated with therapeutic doses may experience exaggerated muscle weakness
  - 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 SPC (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
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 SPC (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.
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.
DISCUSSION WITH THE PATIENT ON BENEFIT/RISK AND AWARENESS OF THE EDUCATIONAL MATERIAL FOR PATIENTS

XEOMIN (Botulinum neurotoxin Type A)
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“).
- Please provide each patient with a Patient Information Sheet prior to injection (see Appendix).
Reporting suspected adverse events

- Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the risk/benefit balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
  
  Mail: HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2  
  Tel: +353 1 676 4971  
  Fax: +353 1 676 2517  
  Website: [www.hpra.ie](http://www.hpra.ie)  
  E-mail: medsafety@hpra.ie

- Adverse events should also be reported to Merz Pharma UK Ltd. Medical Affairs Department (see contact details below)

  Additional copies of the educational materials can be obtained via the Medical Affairs Department (Merz Pharma UK. Ltd.) via [ukdrugsafety@merz.com](mailto:ukdrugsafety@merz.com) or via telephone on +353 (0) 1691 7440
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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 identified risks. Any unauthorized copying or distribution is prohibited
- Contact information:
  Merz Pharma UK Ltd.
  Unit 260, Centennial Park
  Centennial Avenue
  Elstree
  Hertfordshire
  WD6 3SR
  Tel: +353 (0) 1691 7440
  Email: ukdrugsafety@merz.com
Appendix – XEOMIN SPC & Patient Information Sheet

- Attached you can find
  - The XEOMIN SPC
  - The Patient Information Sheet