



## CLINICAL GUIDELINE

# Botulinum Toxin A in Unlicensed Indications in Pathological Muscle Hypertonia, (use of)

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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<b>Does this version include changes to clinical advice:</b>	No
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<b>Approval Group:</b>	Institute of Neurological Sciences Medical Clinical Governance Group

### Important Note:

The Intranet version of this document is the only version that is maintained. Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

**NHS Greater Glasgow and Clyde  
Regional Services - NRU  
Protocol for use of Botulinum toxin A in unlicensed indications in  
pathological muscle hypertonia**

**Background:**

Pathological Muscle Hypertonia as part of disordered motor control, like Spasticity and Dystonia, is common in conditions affecting the brain and spinal cord such as cerebral palsy (CP), acquired brain injury (ABI), stroke (CVA), multiple sclerosis (MS), hereditary spastic paraparesis (HSP), spinal cord injury (SCI) and others. Botulinum toxin A is a recognised treatment for focal spasticity and dystonia. It may be required to gain or prevent loss of function, help manage pain and prevent secondary complications of spasticity. Botulinum toxin A injection is part of a rehabilitation programme involving physical management and/or rehabilitation to achieve an optimal clinical effect.

Spend on botulinum toxin A in NRU was:

- £60,488 in 2017/2018
- £88,678 in 2018/2019
- £121,953 in 2019/2020
- £72,192 in 2020/2021
- £117,501 in 2021/2022

Expenditure is monitored on a regular basis.

**Agent and route:**

Three preparations are available:

- IncobotulinumtoxinA - Xeomin®
- AbobotulinumtoxinA - Dysport®
- OnabotulinumtoxinA - Botox®

Botulinum toxin A is given via an intramuscular injection using electromyographic guidance, electrical muscle stimulation, ultrasound or clinical anatomy.

**License status:**

This protocol has been devised to cover use of Botulinum toxin A in **unlicensed** indications in NRU. Approval of this protocol removes the requirement for individual Unlicensed Medicine (ULM) forms for each patient.

Botulinum toxin A is not licensed for upper or lower limb spasticity in **non-stroke** spasticity in adults and therefore use is “off label” or unlicensed.

Summary of licensed indications for “focal spasticity” in upper and lower limbs

	Licensed status	Licensed status
Preparation	Upper Limb	Lower Limb
Dysport	Post Stroke & TBI	Post stroke & TBI but: IPTR form required see below
Xeomin	Post Stroke	<b>Unlicensed</b>
Botox	Post stroke	Post stroke but: IPTR form required see below

When used for a licensed indication the ULM protocol is not required, however it should be noted that the administration of Dysport and Botox for lower limb use post stroke has not been approved for use by the Scottish Medicines Consortium (SMC) and requires completion of an Individual Patient Treatment Request (IPTR) form.

<p><b>Indications for use</b></p>	<p>Treatment with botulinum toxin A should be considered in patients with focal or multi-focal spasticity / dystonia.</p> <p>Patients should be selected for Botulinum toxin A injections on the basis of:</p> <ul style="list-style-type: none"> <li>• focal or multi-focal clinical problems due to spasticity/dystonia</li> <li>• clearly identified goals for treatment and anticipated clinical gains (taking into account the risks of any negative impact where patients rely on their spasticity for function).</li> </ul>
<p><b>Treatment goals:</b></p>	<p>Common treatment goals for intervention include:</p> <ul style="list-style-type: none"> <li>• reduction of pathological muscle hypertonia</li> <li>• pain relief</li> <li>• reduction of involuntary movements (e.g. associated reactions, spasms)</li> <li>• prevention of contractures and deformity</li> <li>• passive function (making it easier to care for the affected limb)</li> <li>• active function (using the affected limb)</li> <li>• mobility.</li> </ul> <p>Patients will have a thorough and detailed assessment documented prior to receiving treatment. Outcome measure and SMART goals are recorded and reviewed within a month of treatment. Future treatment will be planned in accordance to goals. Treatment will be discontinued if goals are not achieved or if no response (as below).</p>
<p><b>Authorised and designated areas applicable to:</b></p>	<p>Patients may be treated within inpatient or outpatient settings in NHS GGC under the umbrella of Regional Services Directorate.</p>
<p><b>Dose, duration, dilution and administration:</b></p>	<p>The total maximum dose, as suggested by RCP guidelines or SPC for each preparation per treatment session in is as follows:</p> <p><b>Xeomin:</b> Upper limb: 500 units Lower limb: 500 units</p> <p><b>Botox:</b> Upper limb: Botox 360 units Lower limb: 400 units</p> <p><b>Dysport:</b> Upper limb: 1000 units Lower limb: 1500 units</p> <p>Treatment should be started at a low dose of the therapeutic range for the specific muscle to minimise side effects. If an inadequate response is observed, consider a higher dose at next treatment. If a higher dose fails to produce an adequate response, consider switching to alternative brand if treatment is still appropriate. If there are 2 failed responses then the failure protocol as described by Kessler et al (1997) or Hanna et al (1999) should be used (See under references).</p> <p>All new patients requiring botulinum toxin A for an unlicensed indication will receive the most cost-effective brand (currently Dysport and Xeomin). Patients under existing treatment will continue with regular/previously used brand.</p> <p>Injections should be given in one session and re-injections should occur no sooner than 12 weeks after the previous session.</p>

	<p>Where patients are receiving injections between two services, appointments should be co-ordinated so injections are complete within the same week and using the same brand where possible.</p> <p>Refer to RCP guidelines (see under references and Appendix 1) or Delphi Panel guidance for suggested muscle dosing regimes (see under references and Appendix 2).</p>
Potential side effects:	<p><u>Local and distant spread of toxin effect</u></p> <p>Spread of toxin distant from the site of administration has been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.</p> <p>Patients treated with therapeutic doses may also experience exaggerated muscle weakness.</p> <p>Dysphagia has also been reported following injection to sites other than the cervical musculature.</p> <p><u>Patients with pre-existing neuromuscular disorders</u></p> <p>May have an increased sensitivity to agents such as Botulinum Toxin A, which may result in excessive muscle weakness and an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise.</p> <p><u>Hypersensitivity reactions</u></p> <p>If serious (e.g. anaphylactic reactions) and/or immediate hypersensitivity reactions occur, appropriate medical therapy should be instituted.</p> <p><u>Antibody formation</u></p> <p>Too frequent doses may increase the risk of antibody formation, which can result in treatment failure.</p> <p>The potential for antibody formation may be minimised by injecting with the lowest effective dose at the longest intervals between injections as clinically indicated</p> <p><u>Procedure-related injury</u></p> <p>Could occur such as localised infection, pain, inflammation, paraesthesia, hypoesthesia, tenderness, swelling, erythema, and/or bleeding/bruising.</p> <p>Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.</p> <p>Flu like symptoms have also been reported in some patients.</p>
Contraindications for use:	<ul style="list-style-type: none"> <li>• The presence of infection or inflammation at the proposed injection site.</li> <li>• Under active treatment with antibiotic therapy due to infection.</li> <li>• Avoid use in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. Myasthenia Gravis or Lambert-Eaton Syndrome.</li> <li>• Patients who are currently breast feeding.</li> </ul>
Cautions for use:	<p><u>General</u></p> <p>Should be used with caution:</p> <ul style="list-style-type: none"> <li>• in pregnancy (the benefit must outweigh the risks). Note that Botox is not recommended in pregnancy or in women of childbearing potential not using contraception</li> </ul>

	<ul style="list-style-type: none"> <li>• if bleeding disorders of any type occur</li> <li>• in patients receiving anticoagulant therapy or taking other substances that could have an anticoagulant effect.</li> </ul> <p>NB If the patient is taking warfarin then the INR should be taken prior to the treatment and be <math>\leq 2.5</math> on day of injection. If patients target INR needs to be higher than this then liaise with anticoagulation clinic/Haematology.</p> <p>If the patient is taking other anticoagulants (such as apixaban, edoxaban, rivaroxaban, dabigatran), they would continue to take their normal dose. Half the volume of saline should be used to dilute the mixture i.e. 100 units mixed with 1 ml saline and the minimal number of injection sites used.</p> <p><u>Pre existing neurological conditions</u></p> <p>Should only be used with extreme caution and under close supervision in patients with lower motor neurone syndromes (e.g. amyotrophic lateral sclerosis, post-polio syndrome or motor neuropathy).</p> <p>Patients with a history of dysphagia, aspiration or breathing difficulties should be treated with extreme caution. In these patients, treatment must be administered only if the benefit of treatment outweighs the risk.</p> <p>Caution is warranted when injecting in proximity to the lung (particularly the apices) or other vulnerable anatomic structures.</p> <p>Elderly and debilitated patients should be treated with caution.</p> <p>Careful consideration should be given before the injection of patients who have experienced a previous allergic reaction to a product containing botulinum toxin type A. The risk of a further allergic reaction must be considered in relation to the benefit of treatment.</p>
<b>Authorised users:</b>	NRU clinicians, including physicians and physiotherapist non-medical prescribers, who are competent in delivering Botulinum toxin injection therapy for hypertonia management.
<b>Authorised for storage in clinical areas:</b>	Botulinum toxin A should be signed out via the toxin register stored within the controlled drugs cupboard in NRU.
<b>References:</b>	<p>DRESSLER, D., ALTAVISTA, M., ALTENMUELLER, E., BHIDAYASIRI, R., BOHLEGA, S., CHANA, P., CHUNG, T., COLOSIMO, C., FHEODOROFF, K., GARCIA-RUIZ, P., JEON, B., JIN, L., KANOVSKY, P., MILANOV, I., MICHELI, F., ORLOVA, O., PANDEY, S., PIRTOSEK, Z., RELJA, M., SABERI, F. Relja, M. (2021). Consensus guidelines for botulinum toxin therapy: general algorithms and dosing tables for dystonia and spasticity. <i>Journal of Neural Transmission</i>, 128(3), 321-335. <a href="https://doi.org/10.1007/s00702-021-02312-4">https://doi.org/10.1007/s00702-021-02312-4</a></p> <p>ROYAL COLLEGE OF PHYSICIANS 2018. <i>Spasticity in adults: management using botulinum toxin</i>. London. [viewed 28 August 2019]. Available from: <a href="http://www.rcplondon.ac.uk">http://www.rcplondon.ac.uk</a></p> <p>ESQUENAZI, A., ALFARO, A., AYYOUB, Z., CHARLES, D., DASHTIPOUR, K., GRAHAM, G., MCGUIRE, J., ODDERSON, I., PATEL, A. &amp; SIMPSON, D., 2017. OnabotulinumtoxinA Injections for Lower Limb Spasticity: Guidance From a Delphi</p>

	<p>Panel Approach. <i>American Academy of Physical Medicine and Rehabilitation</i>. 9, pp. 960-968. [viewed 15 July 2020]. Available from: <a href="http://dx.doi.org/10.1016/j.pmrj.2016.06.016">http://dx.doi.org/10.1016/j.pmrj.2016.06.016</a></p> <p>SIMPSON, D., PATEL, A., ALFARO, A., AYYOUB, Z., CHARLES, D., DASHTIPOUR, K., ESQUENAZI, A., GRAHAM, G., MCGUIRE, J. &amp; ODDERSON, I., 2017.</p> <p>OnabotulinumtoxinA Injection for Poststroke Upper-Limb Spasticity: Guidance for Early Injectors From a Delphi Panel Process. <i>American Academy of Physical Medicine and Rehabilitation</i>. 9, pp. 136-148. [viewed 15 July 2020]. Available from: <a href="http://dx.doi.org/10.1016/j.pmrj.2017.02.014">http://dx.doi.org/10.1016/j.pmrj.2017.02.014</a></p> <p>HANNA, P., JANKOVIC, J., &amp; VINCENT, A., 1999. Comparison of mouse bioassay and immunoprecipitation assay for botulinum toxin antibodies. <i>Journal of Neurology and Neurosurgical Psychiatry</i>. 66, pp. 612-616.</p> <p>KESSLER, K. &amp; BENECKE, R., 1997. The EBD test- a clinical test for detection of antibodies to Botulinum Toxin type A. <i>Movement Disorders</i>. 12(1), pp. 95-99.</p> <p>Botox, Xeomin and Dysport SPC <a href="https://www.medicines.org.uk/emc/">https://www.medicines.org.uk/emc/</a></p>
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Appendix 1 - RCP guidelines dosing

Upper Limb	Botox/Xeomin* (U)	Dysport (U)
<b>Pectoral girdle</b>		
Trapezius	50-75	200-300
Rhomboid	50-60	200-250
Supraspinatus	40-50	160-200
Infraspinatus	50-60	200-200
Subscapularis	50-80 (B) 15-100 (X)	200-320
Deltoid	50-75 (B) 20-150 (X)	200-300
<b>Shoulder</b>		
Pectoralis major	75-100 (B) 20-200 (X)	300-400
Pectoralis minor	40	150-160
Latissimus dorsi	60-80 (B) 25-150 (X)	240-320
Teres major	30-50 (B) 20-100 (X)	120-200
Teres minor	30-50	120-200
Serratus anterior	60-70	250-270
Coracobrachialis	30-50	120-200
<b>Elbow flexors</b>		
Biceps brachii	75-100	100-300
Brachialis	50-75	200-400
Brachioradialis	50-60	200-240
<b>Forearm</b>		
Pronator quadratus	20-30	75-120
Pronator teres	30-40	120-160
Supinator	30-40	120-160
<b>Wrist flexors</b>		
Flexor carpi radialis	30-40	120-160
Flexor carpi ulnaris	30-40	120-160
<b>Finger flexors</b>		
Flexor digitorum superficialis	25-30	100-120
Flexor digitorum profundus	30-40	120-160
<b>Thumb flexors</b>		
Flexor pollicis longus	20-30	75-120
Flexor pollicis brevis	(SPC 5-30)	-
Opponens pollicis	(SPC 5-30)	-
Adductor pollicis	20-40	75-100
<b>Elbow extensors</b>		
Triceps	75-100	300-400
<b>Wrist extensors</b>		
Extensor carpi ulnaris	30-40	120-160
Extensor carpi radialis longus	30-40	120-160
Extensor carpi radialis brevis	20-30	75-120
<b>Finger extensors</b>		
Extensor digitorum communis	30-40	120-160
Extensor digiti minimi	30-40	120-160
Extensor indicis	20-30	75-120
<b>Thumb extensors</b>		
Extensor pollicis longus	20-30	75-120
Extensor pollicis brevis	20-25	75-100

Lower limb	Botox/Xeomin* (U)	Dysport (U)
<b>Hip flexors</b>		
Psoas major	100-200	600-800
Iliacus	75-150	200-400
<b>Lateral vertebral column flexion</b>		
Quadratus lumborum	100	400
<b>Hip adductors</b>		
Adductor magnus, Adductor longus, Adductor brevis	100-200 (between whole Adductor group)	400-750 (between whole Adductor group)
Gracilis	80-120	300-400
Pectineus	50-100	200-400
<b>Internal rotation of hip</b>		
Gluteus maximus	-	-
Gluteus medius	100	400
Gluteus minimus	-	-
<b>Knee flexors</b>		
Semitendinosus, Semimembranosus	100-150 100-150	400-600 400-500
Biceps femoris long head and short head	100-150	400-600
Popliteus	25-30	100-120
<b>Knee extensors</b>		
Rectus femoris	100-150	400-500
Vastus medialis, intermedius and vastus lateralis	100-150	400-500
Sartorius	-	-
<b>Plantar flexors</b>		
Gastrocnemius medial head	50-100	200-400
Gastrocnemius lateral head	50-100	200-400
Soleus	75-100	300-400
Tibialis posterior	50-80	200-320
<b>Foot</b>		
Tibialis anterior	75-120	300-400
Peroneus tertius	30-40	120-150
Peroneus longus	50-80	200-320
Peroneus brevis	30-40	120-160
Extensor digitorum longus	50-75 (B) 50-80 (X)	200-300
Extensor hallucis longus	50-60	200-250
Flexor digitorum longus	40-60	160-200
Flexor digitorum brevis	10-20	40-80
Flexor hallucis longus	40-60	160-240
Flexor hallucis brevis	10-20	40-80
Adductor Hallucis	10-20	40-80

\* Xeomin doses same as Botox unless stated



## Appendix 2

Delphi panel approach to treating most common UL postures:

UL posture;	Muscles	Dose range (U)	Total dose used (U)
Adducted and IR shoulder	<b>Pectoral complex</b>	75-100	100-200
	<b>Latissimus Dorsi</b>	75	
	Teres Major	50-75	
	Deltoid	20	
	Brachialis	75	
	Levator scapulae	30	
Flexed elbow	<b>Brachioradialis</b>	25-50	100-150
	<b>Biceps</b>	0-50	
	<b>Brachialis</b>	50-100	
	Pronator teres	38-100	
Pronated forearm	<b>Pronator quadratus</b>	0-25	50-100
	<b>Pronator teres</b>	45-60	
	Flexor carpi radialis	20	
	Brachialis	100	
	Brachioradialis	25	
Flexed wrist	<b>Flexor carpi radialis</b>	50-75	60-100
	<b>Flexor carpi ulnaris</b>	25-50	
	Palmaris longus	13-50	
	Flexor pollicis longus	20-75	
	Flexor digit superficialis	25-75	
	Flexor digit profundus	25-75	
Flexed fingers	<b>Flexor digit superficialis</b>	20-60	50-100
	<b>Flexor digit profundus</b>	25-75	
	Flexor carpi radialis	30	
	Flexor carpi ulnaris	30	
	Lumbricals	30	
Thumb-in-palm	<b>Flexor pollicis longus</b>	40-50	50-75
	<b>Adductor pollicis</b>	10-20	
	<b>Flexor pollicis brevis</b>	12.5-20	
	Flexor digit profundus	35	

Delphi panel approach to treating most common LL postures:

LL posture;	Muscle	Dose range (U)	Total dose (U)
Adducted thigh	<b>Adductor magnus</b>	75-150	150-200
	<b>Adductor longus</b>	75-80	
	<b>Adductor brevis</b>	20-25	
	Gracilis	25-40	
	Iliopsoas	25-150	
	Medial hamstrings	50	
Flexed knee	<b>Medial hamstrings</b>	125	100-200
	<b>Lateral hamstrings</b>	75	
	Gastrocnemius	50-200	
	Iliopsoas	40-150	
	Tensor fascia lata	25-150	
	Medial Hamstrings	50	
Extended knee	<b>Rectus femoris</b>	80-125	125-200
	<b>Vastus lateralis</b>	50-70	
	<b>Vastus medialis</b>	50	
	Vastus intermedialis	35-75	
	Gluteus maximus	40	
Equinovarus foot	<b>Tibialis posterior</b>	100	250-300
	<b>Gastrocnemius</b>	125	
	<b>Soleus</b>	75-100	
	Tibialis anterior	75	
	Flexor digitorum longus	20-75	
	Flexor digitorum brevis	13-38	
	Flexor hallucis longus	25-38	
	Extensor hallucis longus	13-50	
Plantar flexed foot	<b>Gastrocnemius</b>	125	200
	<b>Soleus</b>	75	
	Tibialis posterior	25-75	
	Long toe flexors	20	
Striated toe	Extensor hallucis longus	50	50
	Extensor hallucis longus (motor point)	38	
	Flex digitorum longus	25-30	
Flexed toes	<b>Flexor digitorum longus</b>	50-80	100-125
	<b>Flexor digitorum brevis</b>	25	
	<b>Flexor hallucis longus</b>	40-50	
	Flexor hallucis brevis	13	