Bedfordshire and Luton Joint Prescribing Committee (JPC)

February 2017
Review February 2020

Bulletin 244:- Botulinum toxin A use in the acute setting in corneal patients to induce ptosis to prevent corneal perforations and in ectropion patients who are not suitable for surgery due to other co-morbidities.

JPC Recommendations:-

- To support use in the acute setting i.e. **in corneal patients to induce temporary ptosis to prevent corneal perforations.**
- To support use in the chronic setting i.e. **in ectropion patients who are not suitable for surgery due to other co-morbidities** and who fit the following patient selection criteria:-
  - Patients with reduced mental capacity e.g dementia, learning difficulties.
  - Patients taking NOACS or other anticoagulants which cannot be stopped temporarily for surgery, for whom there would be an increased risk of retrobulbar haemorrhage (and subsequent visual loss) with surgery.
  - Patients with physical constraints e.g spinal/ back problems, who cannot lie in one position for the duration of surgery.

The above recommendations are subject to administration of the Botulinum toxin being charged to CCGs using the following:

- The Luton & Dunstable Hospital – Outpatient Procedure tariff
- All other Trusts – Outpatient Appointment tariff

New Medicine Review – Bulletin - Botulinum toxin A use in the acute setting in corneal patients to induce ptosis to prevent corneal perforations and in ectropion patients who are not suitable for surgery due to other co-morbidities.

Medicine	Botulinum toxin type A
Document status	*Final*
Date of last revision	22 February 2017
Proposed Sector of prescribing	Acute
Introduction	The Luton & Dunstable Hospital has asked the JPC to review the use of botulinum toxin A in the acute setting in corneal patients to induce ptosis to prevent corneal perforations and in ectropion patients who are not suitable for surgery due to other co-morbidities.
Summary	Protection of the cornea is essential in patients with inadequate eyelid coverage, as may occur in Graves disease or facial nerve (CN VII) dysfunctions such as Bell palsy. It can also be used to aid in the healing of indolent corneal ulceration sometimes seen with tear-film deficiency, herpes simplex or zoster, stem cell dysfunction, or CN V dysfunction (neurotrophic lesions). [1, 2] Ectropion is a condition in which the eyelid (usually the lower eyelid) becomes slack and is no longer in contact with the eyeball. The commonest cause is loss of elasticity and muscle tone of the eyelids which happens as part of the ageing process. The affected eye becomes sore, red and watery. Ectropion may also cause conjunctivitis, exposure of the cornea with irritation and potentially corneal infections. Patients may be helped by artificial tears and unmedicated ointments. If the eye does not close fully at night, it may need to be taped shut. Sometimes a bandage contact lens is fitted to protect the eye surface from drying. If these measures do not help, one of a number of possible surgical operations, usually carried out under local anaesthetic, may solve the problem. [3, 4] Surgical Tarsorrhaphy is the only other alternative to Botulinum toxin and involves surgical fusion of the upper and lower eyelid margins. According to the American Academy of Ophthalmology it is one of the safest and most effective procedures for healing difficult-to-treat corneal lesions. Tarsorrhaphy is most commonly performed to protect the cornea from exposure. Tarsorrhaphies may be temporary or permanent; in the latter case, raw tarsal edges are created to form a lasting adhesion. They may be total or partial, depending on whether all or only a portion of the palpebral fissure is occluded. Tarsorrhaphies are also classified as lateral, medial, or central, according to the position in the palpebral fissure. The cosmetic effect of a lateral tarsorrhaphy is significant, and patients are often unhappy with the appearance afterward as it can lead to scarring of the eyelid margin and is cosmetically disfiguring. [1, 2, 5] Botulinum toxin blocks acetylcholine release causing denervation of the muscle fibres for several weeks. Infiltration of botulinum toxin A in the levator palpebrae superioris muscle in the eye results in a temporary ptosis. Muscle

	activity returns to pre-injection levels as new motor end plates are formed over 6 to 8 weeks. Botulinum toxin does not induce scar tissue formation. [5] The use of botulinum toxin A to induce ptosis is based on case reports, case series and prospective open label studies. Use of botulinum toxin A is a widely accepted method of inducing a temporary protective ptosis and this has occurred for nearly 30 years. The 2 formulations which have been used in the studies are Dysport and Botox. Botox has been used in relatively low doses (2.5 and 5 units) and given up to 4 times. Dysport has also been given similarly in low doses (2.5 and 5 units) given on 3 or 4 occasions but also has been given in larger single doses (24-100 units). The evidence has evolved over time to show that a larger dose given in specific locations (e.g. anterior levator palpebrae superioris, Muller muscle) or transconjunctivally into the subconjunctival space is more likely to achieve complete ptosis and less likely to induce adverse effects e.g. transient superior rectus underaction and diplopia. [2, 5-10] Based on the doses used in the studies, Dysport is a more cost effective option than Botox. Administration of botulinum toxin A would require an outpatient clinic appointment. [11, 12] I have not found any information on cost effectiveness analyses of this procedure.
Key points **Evidence level**	• ***Protection of the cornea is essential in patients with inadequate eyelid coverage and to prevent corneal perforations.*** • ***Treatment options are artificial tears and unmedicated ointments. If the eye does not close fully at night, it may need to be taped shut. A bandage contact lens can be fitted to protect the eye surface from drying. Tarsorrhaphy is the surgical fusion of the upper and lower eyelid margins and is a safe and effective procedure for healing difficult-to-treat corneal lesions by protecting the cornea from exposure. Specialists have indicated that this is the most appropriate comparator treatment option to Botulinum toxin A.*** • ***The cosmetic effect of a lateral tarsorrhaphy is significant, and patients are often unhappy with the appearance afterward as it can lead to scarring of the eyelid margin and is cosmetically disfiguring.*** • ***The use of botulinum toxin A (Botox and Dysport) to induce ptosis is based on case reports, case series and prospective open label studies conducted over the last 30 years.*** • ***The evidence has evolved over time to show that a larger dose given in specific locations (e.g. anterior levator palpebrae superioris, Muller muscle) or transconjunctivally into the subconjunctival space is more likely to achieve complete ptosis and less likely to induce adverse effects e.g. transient superior rectus underaction and diplopia.*** • ***Dysport has a lower acquisition cost than Botox. Administration would require an outpatient appointment.*** • ***There are no cost effectiveness studies for botulinum toxin and this indication.*** Level 4
The intervention	The intervention is botulinum toxin type A.

Mechanism of action	The active constituent in botulinum toxin type A is a protein complex derived from *Clostridium botulinum*. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin. It works by blocking the release of neurotransmitters (e.g. peripheral acetylcholine release at presynaptic cholinergic nerve terminals) and sensory pathways. [13]
Licensed indication	Botulinum toxin type A has a number of licensed indications [11, 13-18] – • Treatment of focal spasticity (including hand and wrist disability associated with stroke) • Blepharospasm • Hemifacial spasm • Spasmodic torticollis • Severe hyperhidrosis of the axillae • Prophylaxis of headaches in adults with chronic migraine • Temporary improvement of moderate to severe wrinkles between the eyebrows in adults under 65 years • Ankle disability due to lower limb spasticity associated with stroke • Management of bladder dysfunctions • Temporary improvement of moderate to severe crow's feet The indication being considered for this review is unlicensed.
Formulation/ Available Products	There are 6 botulinum toxin type A products available as powder for reconstitution for injection [13-18] – • Azzalure, Galderma (U.K) Ltd • Bocouture 50 units powder for solution for injection, Merz Pharma UK Ltd • BOTOX 50, 100, 200 Units, Allergan Ltd • Dysport 300, 500 units, Ipsen Ltd • Vistabel, Allergan Ltd • Xeomin 50, 100, 200 Units powder for Solution for Injection, Merz Pharma UK Ltd These products are licensed to given by subcutaneous, intradermal or intramuscular injection.
Usual dosage	The studies (see below) have all used different doses. Dysport: 2.5, 5, 10, 24, 30, 50, 100 Botox: 2.5, 3, 5 (may be given multiple times to give total of 10-15 units) The doses are given by different routes compared to the product licences e.g. transconjunctival supratarsal injection, transcutaneous injection.
Treatment alternatives / place in therapy	Artifical tears and unmedicated ointments. Bandage contact lenses. Taping eyelids shut. Surgical tarsorrhaphy [2, 5, 7, 8] Specialists have indicated that the most appropriate treatment alternative to Botulinum toxin A is surgical tarsorrhaphy.
Future alternatives	None known.
National guidance	None found.
Local Guidance	None found.
Evidence for use	A prospective, open label in 15 patients in 1987 used 2.5 units botulinum toxin A (Dysport) in 11 patients and 5 units in 4 patients. The botulinum was injected just beneath the superior orbital margin. A maximum of 4 injections were administered. The time taken for maximum ptosis to develop ranged

from 30 hours to 10 days (mean 3 days). Ptosis was complete in 8 patients. Complete corneal coverage occurred in a further 3 patients. Mean ptosis lasted 7 days to 5 weeks (mean 2.5 weeks). On average recovery took 8.1 weeks (maximum of 7 months). In 10 cases further injections were given because continuing protection was necessary or healing was not complete. Progression of the underlying condition was seen in 4 cases despite adequate corneal coverage. The most common complication was underactivity of the ipsilateral superior rectus muscle (12 cases) and lasted a mean of 6 weeks. Diplopia occurred in 2 patients. Haemorrhage at the site of injection occurred in 1 patient. Patient acceptability of the procedure was high. [5]

A case series of 25 patients who were being considered for surgical tarsorrhaphy were given botulinum toxin A instead. 21 patients had indolent ulceration and 4 required prophylaxis for neuroparalytic keratitis. After administration of 2.5 units of botulinum toxin A (Dysport) complete ptosis was reported in 15 patients after 1 injection (60%), a further 3 patients experienced complete ptosis after another dose. The time to complete ptosis was a mean of 3.6 days (range 1-10) and the duration was a mean of 16 days (range 7-35). Complete healing was seen in 19 eyes in a mean of 10 days (range 4 -77). Transient underaction of the ipsilateral superior rectus muscle was seen in 17 patients for 3-20 weeks (mean of 6 weeks). Three patients experienced diplopia as the levator muscle function returned. Haemorrhage at the site of injection occurred in 1 patient. [6]

An open label prospective multicentre study evaluated the safety and efficacy of botulinum toxin A (Botox) to produce a protective ptosis in patients where a surgical tarsorrhaphy would otherwise be required. Twenty one patients were enrolled and included in the safety analysis, 16 were included in the efficacy analysis (3 patients were given a 2nd injection before the effects of the first were analysed and therefore not eligible for the efficacy analysis and 2 patients had incomplete or missing data). Doses of 2.5 and 5 units were injected into the levator palpebrae superioris muscle through the eyelid. Patients were followed daily until ptosis occurred and monitored 1-2 weekly until the ptosis resolved. Injections were repeated if necessary until the underlying condition had healed. Ptosis occurred in an average of 4 ± 0.5 days (range 2-8). Duration of ptosis was an average of 46 ± 12.1 days (range 1-206). 2.5 units was not adequate to produce sufficient ptosis so the most effective dose was 5 units. The underlying corneal condition resolved in 14 patients, for 2 patients surgical intervention was required. Ocular lubricants were required in 18 patients to assist corneal healing. It was observed that patients confined to a supine position did not have as effective protection as mobile patients. Vertical diplopia was the only treatment adverse event reported in 5/21 patients (24%) with good vision. The diplopia resolved without any additional intervention. The authors note that caution should be exercised in using Botox-induced ptosis in eyes with good vision as diplopia may be a significant problem. [7]

A prospective interventional case series in 10 patients (10 eyes) evaluated the effectiveness of anterior chemodenervation of the levator palpebrae superioris with botulinum toxin A (Botox) to induce temporary ptosis for corneal protection and assessed the incidence of superior rectus underaction. The patients had diagnoses of persistent epithelial defect or Bells palsy and all required temporary tarsorrhaphy for cornea protection. The median age was 30 years old (range 4-57). Each patient had one

	injection and the median dose was 12.5 units (range 10-15). Patients also continued on appropriate topical medications as prescribed by the corneal surgeon. Ptosis was measured by the change in mean palpebral fissure height. Before Botox, the mean height was 9 ± 2.1mm and 1 week after it was reduced to 2.8 ± 1.9mm (70.4 ± 17.4%) reduction. The mean difference was 6.2mm (95% CI 4.9-7.4mm) and considered statistically significant (p=0.005). Nine patients had >50% reduction in palpebral fissure height (90%, 95% CI 71.4-100%) 1 week after injection; 7/9 patients (77.8%, 95% CI 50.6-100%) at week 2 and 2/9 patients (22.2%, 95% CI 0-49%) at week 4. The fissure height returned to the pretreatment level after a mean of 9.2 weeks (range 5-16). Corneal pathology improved in all cases. No adverse effects were observed. The authors note that as a higher initial dose was given, repeat injections were not required and anterior placement of the injection prevented superior rectus underaction. [2] 3 case reports describe use of botulinum toxin A chemodenervation. Two patients (75 year old female and 40 year old male) required corneal protection after failure of medical treatment. The female patient strongly desired nonsurgical treatment due to comorbid medical conditions (not specified) and potential scarring. The male patient desired nonsurgical tarsorrhaphy to allow potential healing of a corneal graft. Both patients were given 2 injections of Dysport – 24 units to the Muller muscle on the underside of the upper eyelid and 24 units to the levator palebrae superioris under the orbital rim. Ptosis developed over 3 days in the female and 2 days in the male. The third patient was a 46 year old female with Bells palsy. 3 units of Botox was injected into the Muller muscle, at 7 days the patient reported greatly improved facial symmetry and eyelid positioning due to slight eyelid ptosis induced by chemodenervation. No adverse effects are noted. [8]
Safety*	Adverse effects noted in the case studies and series included diplopia and transient superior rectus underaction. [5-7]. Transient superior rectus underaction has been reported in 68-80% of treated patients. [5, 6] 3 case reports published in 1994 highlight permanent superior rectus weakness following botulinum toxin administration which required corrective strabismus surgery. A possible reason for this is pre-existing latent vertical deviation. The report authors suggest the incidence of permanent superior rectus weakness could be as high as 1.5%. [9] A retrospective review of ophthalmic clinical records for 15 patients administered botulinum toxin A (Dysport) to induce protective upper eye lid ptosis compared the incidence of superior rectus underaction when given transconjunctivally into the subconjunctival space (Group A) with 20 patients in a previous study the authors had undertaken where Dysport had been given transcutaneously through the upper eyelid crease (Group B). All the patients had acute exposure keratopathy. In group A the mean age was 55.4 years. The mean number of Dysport units injected was 54.8 (range 6-125, mode 50). The figures are skewed by 2 patients, one of whom had 6 units of Botox and not Dysport and one who had 125 units due to severe keratopathy. If these 2 outliers are excluded the average dose was 53 units (range 30-100). Two patients (13.3%) had reduced upgaze due to diffusion of botulinum toxin A to the superior rectus muscle. One patient (6.67%) required treatment for diplopia lasting 12 months or more. In comparison, the mean age in group B was 50.2 years and each patient received 10 units to induce protective ptosis. Nine patients (45%) had reduced upgaze due to

<table>
<tr><td></td><td>diffusion of botulinum toxin A to the superior rectus muscle. Five patients (25%) required treatment for diplopia lasting 12 months or more. The difference in incidence of reduced upgaze between the 2 techniques is statistically significant, p=0.0493. The study authors conclude that the higher doses given subconjunctivally are safe as they are less likely to interfere with the superior rectus muscle and they are effective as the desired level of ptosis can be produced in most cases in the first instance. [10]</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Costs
[BNF Oct 2016]</td><td>
<table>
<tr><th>Drug & Dosage</th><th>Cost per dose</th><th>Total cost of multiple doses (course)</th></tr>
<tr><td>Botox 2.5, 5 units</td><td>2.5 units = £3.88
5 units = £7.75</td><td>10 units = £15.50
15 units = £23.25</td></tr>
<tr><td>Dysport 2.5, 5, 10 24, 30, 50, 100 units</td><td>2.5 units = £0.77
5 units = £1.54
10 units = £3.08
24 units = £7.40
30 units = £9.24
50 units = £15.40
100 units = £30.80</td><td>7.5 units = £2.31
10 units = £3.08
12.5 units = £3.82</td></tr>
</table>
N.B. Doses are for general comparison and do not imply therapeutic equivalence.</td></tr>
<tr><td>Tariff status</td><td>Procedure not in Tariff. [12]</td></tr>
<tr><td>Activity costs</td><td>An ophthalmology outpatient clinic appointment cost varies from £113-£125 for the first visit to £64-£94 for further visits (the increased costs are based on >1 health care professional being involved with treatment). [12]</td></tr>
<tr><td>Cost effectiveness (if available)</td><td>No papers found on cost effectiveness.</td></tr>
<tr><td>Potential number of patients in Bedfordshire & Luton</td><td>Approximately 12 patients per year.</td></tr>
<tr><td>Impact per 100,000 population</td><td>Impact per 100, 000- to be discussed at JPC.</td></tr>
<tr><td>Affordability considerations</td><td>Botulinum toxin A injections – maximum of 4 injections per patient per year. Surgical tarsorrhaphy is £559 for procedure and then a further £559 to reverse procedure. The cost of surgical tarsorrhaphy is higher than treatment with botulinum toxin A injection, assuming that the patient does not have more than 1 year treatment with Botulinum Toxin A?</td></tr>
</table>

Decisions from other bodies **Comments sought from –**	None found Other CCGs in East of England – no one else has looked at this use of botulinum toxin.
Evidence strengths and limitations	**Strengths** The evidence has evolved over time to show that a larger dose given in specific locations or via particular routes is more likely to achieve complete ptosis and less likely to induce adverse effects. **Limitations** The evidence is all based on prospective open label case series, case reports and retrospective analysis with small sample sizes. All of the evidence is non comparative with the alternative of surgical tarsorrhaphy. Some of the reports conclude that the results need to confirmed in larger randomised controlled studies.

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

**Consult Summary of Prescribing Characteristics for full prescribing detail.*
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

References

1. American Academy of Ophthalmology. Tarsorrhaphy. Website accessed 28/10/2016 http://www.aao.org/bcscsnippetdetail.aspx?id=3c2b27d8-c930-4a31-8036-9ce3dcebaf61
2. Naik MN; Gangopadhyay N; et al. Anterior chemodenervation of levator palpebrae superioris with botulinum toxin type-A (Botox) to induce temporary ptosis for corneal protection. Eye 2008; 22 (9): 1132-1136.
3. College of Optometrists . Ectropion. Version 5, Date of publication 06/08/2015 http://www.college-optometrists.org/en/utilities/document-summary.cfm/9F658DC9-3E84-4762-846E6DC605A1F478
4. Zucker JL. The eyelids: Some common disorders seen in everyday practice. Geriatrics 2009; 64 (4): 14-19+28.
5. Adams GG, Kirkness CM, Lee JP. Botulinum toxin A induced protective ptosis. Eye (London) 1987; 1: 603-608
6. Kirkness CM, Adams GG, Dilly PN, Lee JP. Botulinum toxin A-induced protective ptosis in corneal disease. Ophthalmology 1988; 95: 473-80
7. Ellis MF; Daniell M. An evaluation of the safety and efficacy of botulinum toxin type A (BOTOX) when used to produce a protective ptosis. Clinical & experimental ophthalmology 2001; 29 (6): 394-399.
8. Reddy UP; Woodward JA. Abobotulinum toxin a (Dysport) and botulinum toxin type a (Botox) for purposeful induction of eyelid ptosis. Ophthalmic Plastic and Reconstructive Surgery 2010; 26 (6): 489-491.
9. Heyworth PL, Lee JP. Persisting hypotropias following protective ptosis induced by botulinum neurotoxin. Eye (London) 1994; 8: 511-515
10. Sadiq SA.; Dharmasena A. Superior rectus underaction following botulinum toxin injection to induce protective upper eye lid ptosis-a comparative study of two techniques. Strabismus 2014; 22 (3): 111-114.
11. British National Formulary, October 2016. Accessed via www.medicinescomplete.nhs.uk
12. NHS England. 2016/17 National Prices and National Tariff Workbook. https://www.gov.uk/government/publications/nhs-national-tariff-payment-system-201617
13. Botox 50, 100, 200 Units Summary of Product Characteristics. Allergan Ltd. Last Updated on eMC 30/03/2015

14. Azzalure Summary of Product Characteristics. Galderma (U.K) Ltd. Last Updated on eMC 20/11/2015
15. Bocouture 50 units powder for solution for injection Summary of Product Characteristics. Merz Pharma UK Ltd. Last Updated on eMC 17/05/2016.
16. Dysport 300, 500 units Summary of Product Characteristics. Ipsen Ltd. Last Updated on eMC 28/06/2016.
17. Vistabel Summary of Product Characteristics. Allergan Ltd. Last Updated on eMC
18. Xeomin 50, 100, 200 Units powder for Solution for Injection Summary of Product Characteristics. Merz Pharma UK Ltd. Last Updated on eMC 19/07/2016.

Appendix 1- Search Strategy

BNF, search term = botulinum toxin type a
Electronic Medicines Compendium, search term = botulinum toxin type a, ptosis, ectropion
Martindale, search term = botulinum toxin type a, ptosis, ectropion
American Hospital Formulary Service Drug Information Manual, search term = botulinum toxin type a, ptosis, ectropion
DrugDex, search term = botulinum toxin type a, ptosis, ectropion
Ophthalmic Drugs, search term = botulinum toxin type a, ptosis, ectropion
Moorfields Eye Hospital Formulary, search term = botulinum toxin type a, ptosis, ectropion
NHS Evidence, search term = botulinum toxin type a, ptosis, ectropion
Cochrane Library = botulinum toxin type a, ptosis, ectropion
PubMed = botulinum toxin type a, ptosis, ectropion
UKMI Prescribing Outlook New Medicines 2016 = botulinum toxin type a, ptosis, ectropion
SPS website = botulinum toxin type a, ptosis, ectropion
NHS Economic Evaluations Database = botulinum toxin type a, ptosis, ectropion
Payment by Results Tariff 2016-2017 = botulinum toxin type a, ptosis, ectropion

Medline
1. Medline; exp BOTULINUM TOXINS, TYPE A/; 7180 results.
2. Medline; exp BLEPHAROPTOSIS/; 5071 results.
3. Medline; exp CORNEAL PERFORATION/; 174 results.
4. Medline; 2 AND 3; 0 results.
5. Medline; 1 AND 3; 0 results.
6. Medline; 1 AND 2; 81 results.
7. Medline; exp ECTROPION/; 1022 results.
8. Medline; 1 AND 7; 5 results.

Embase
9. EMBASE; exp BOTULINUM TOXIN A/; 17035 results.
10. EMBASE; exp PTOSIS/; 14665 results.
11. EMBASE; exp CORNEA PERFORATION/; 1658 results.
12. EMBASE; 10 AND 11; 16 results.
13. EMBASE; 9 AND 12; 0 results.
14. EMBASE; induce.ti,ab; 440843 results.
15. EMBASE; 10 AND 14; 141 results.
16. EMBASE; 9 AND 15; 15 results.
17. EMBASE; 9 AND 11; 1 results.
18. EMBASE; exp ECTROPION/; 2350 results.
19. EMBASE; 9 AND 18; 59 results.
20. EMBASE; exp ECTROPION/dt, th [dt=Drug Therapy, th=Therapy]; 100 results.
21. EMBASE; 9 AND 20; 5 results.

Treatment assessed (November 2016 and February 2017):
Botulinum toxin A use in the acute setting in corneal patients to induce ptosis to prevent corneal perforations and in ectropion patients who are not suitable for surgery due to other co-morbidities.

JPC Recommendations:-

- To support use in the acute setting i.e. **in corneal patients to induce temporary ptosis to prevent corneal perforations.**
- To support use in the chronic setting i.e. **in ectropion patients who are not suitable for surgery due to other co-morbidities** and who fit the following patient selection criteria:-
    - Patients with reduced mental capacity e.g dementia, learning difficulties.
    - Patients taking NOACS or other anticoagulants which cannot be stopped temporarily for surgery, for whom there would be an increased risk of retrobulbar haemorrhage (and subsequent visual loss) with surgery.
    - Patients with physical constraints e.g spinal/ back problems, who cannot lie in one position for the duration of surgery.

The above recommendations are subject to administration of the Botulinum toxin being charged to CCGs using the following:

- The Luton & Dunstable Hospital – Outpatient Procedure tariff
- All other Trusts – Outpatient Appointment tariff

1) Clinical Effectiveness

The use of botulinum toxin A to induce ptosis is based on case reports, case series and prospective open label studies. Use of botulinum toxin A is a widely accepted method of inducing a temporary protective ptosis and this has occurred for nearly 30 years. The 2 formulations which have been used in the studies are Dysport and Botox. Botox has been used in relatively low doses (2.5 and 5 units) and given up to 4 times. Dysport has also been given similarly in low doses (2.5 and 5 units) given on 3 or 4 occasions but also has been given in larger single doses (24-100 units). The evidence has evolved over time to show that a larger dose given in specific locations (e.g. anterior levator palpebrae superioris, Muller muscle) or transconjunctivally into the subconjunctival space is more likely to achieve complete ptosis and less likely to induce adverse effects e.g. transient superior rectus underaction and diplopia.

2) Cost Effectiveness

No cost-effectiveness studies were identified.
The cost per patient is dependent on the preparation, dose used and the frequency of administration, but the higher cost is related to activity (Ophthalmology out patient appointment rather than drug costs.). These costs range from £305 - £407 per patient per year (assuming 4 Botulinum Toxin A dose administrations per year). This compares with £559 for surgical

tarsorrhaphy and then a further £559 to reverse procedure should this be required.
3) Equity No Equity issues were identified.
4) Needs of the community The Luton and Dunstable Hospital estimate 12 patients per year will require this treatment.
5) Need for healthcare (incorporates patient choice and exceptional need) Other treatment options are artifical tears and unmedicated ointments, bandage contact lenses, taping eyelids shut and surgical tarsorrhaphy, Specialists have indicated that the most appropriate alternative treatment option is surgical tarsorrhaphy.
6) Policy drivers None
7) Disinvestment May avoid the need for surgery (TBC)

The JPC agreed the following sections within the PCT Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*