JPC Recommendation:

The Committee agreed to support the use of Botulinum A (Onabotulinum toxinA) to treat over active bladder in men and women in accordance with NICE Clinical Guidelines (CG 148, issued August 2012, CG 40, issued 2006 and CG 97, issued 2010):-

Urinary incontinence in neurological disease (CG 148 issued August 2012)
Offer bladder wall injection with BTX-A to adults with spinal cord disease (e.g. SCI or MS) and with symptoms of an overactive bladder or with urodynamic investigations showing impaired bladder storage, and in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

- Ensure that patients who have been offered continuing treatment with repeated BTX-A injections have prompt access to repeat injections when symptoms return.

- Before offering bladder wall injection with BTX-A: explain to the person and/or their family members and carers that a catheterisation regimen is needed in most people with neurogenic lower urinary tract dysfunction after treatment, and ensure that they are able and willing to manage such a regimen should urinary retention develop after the treatment.

Urinary incontinence in women (CG 40 issued 2006)
Bladder wall injection with BTX-A should be used in the treatment of idiopathic detrusor overactivity only in women who have not responded to conservative treatments, and who are willing and able to self-catheterise. Women should be informed about the lack of long-term data. There should be special arrangements for audit or research.

Lower urinary tract symptoms in men (CG 97 issued 2010) Consideration should be given to offering bladder wall injection with BTX-A to men with detrusor overactivity only if their symptoms have not responded to conservative management and drug treatments and the man is willing and able to self-catheterise.
# Proposed Sector of prescribing

<table>
<thead>
<tr>
<th>Introduction</th>
<th>Urology</th>
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<td>Summary Key points</td>
<td>Overactive bladder (OAB) syndrome is a common condition characterised by urgency, with or without urge incontinence, frequency and nocturia. It is often divided into two types: neurogenic, where the symptoms are secondary to an underlying neurological condition such as spinal cord lesions, multiple sclerosis (MS) or Parkinson’s disease; and idiopathic, where there is no discernable pathology underlying the symptoms. OAB has been shown to decrease health related quality of life (QOL) and lead to increased levels of depression and anxiety, as well as having a significant financial burden.¹</td>
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<td>Evidence level</td>
<td>Evidence level</td>
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<td>First line treatment consists of behavioural and lifestyle modifications which may be supplemented with antimuscarinic drugs, and in some cases, clean intermittent catheterisation (CIC). Anti-muscarinic drugs can improve symptoms but are often poorly tolerated, and often cause patients to discontinue treatment. More invasive treatment options used as second or third line therapies include pudendal or sacral nerve stimulation, augmentation cystoplasty, bladder instillation of vanilloids (resiniferatoxin), and intravesical injection of botulinum toxin.¹</td>
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<td>Evidence level</td>
<td>There are seven serotypes of botulinum toxin, A to G, of which the most commonly used is botulinum toxin type A (BTX-A), and which was the first licensed serotype in clinical use under the trade name Botox. Other brands of BTX-A in use include Dysport. The different companies manufacturing BTX-A have different isolation, extraction, purification, and formulation processes, and therefore different fragments of botulinum toxin are isolated. Although the BTX-A products are of the same serotype, their dose, efficacy, duration of effect, and safety profile are different enough for them not to be considered generic equivalents. There are no randomised studies directly comparing the different agents for dose, efficacy, and safety for the different indications of use and consequently, it can be problematic to assume a direct dose correlation. However, 1 U of Botox has been shown, in small studies, to be approximately similar in terms of efficacy to 3–5 U of Dysport. New terminology has been approved for the different botulinum toxin, preparations and of the BTX-A products, Botox is now called onabotulinumtoxinA and Dysport, abobotulinumtoxinA. The changes to the established drug names, enforced by the FDA, were made to reinforce individual potencies, to prevent drug errors, and to prevent interchangeability of products.²</td>
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<td>Evidence level</td>
<td>BTX-A is being increasingly used to treat severe OAB refractory to standard management; and there is a large body of evidence demonstrating its effectiveness in the short term. OnabotulinumtoxinA has been more comprehensively evaluated in this setting than abobotulinumtoxinA,² and only the former (Botox⁶) is licensed for urological use; specifically for the management of urinary incontinence in adult patients with neurogenic detrusor overactivity due to subcervical spinal cord injury (traumatic or non-traumatic) or MS, who are not adequately managed with anticholinergics; patients should be already catheterising or willing and able to catheterise if required. The licensed dose is 200 Units which cannot be readministered within 3 months, though median interval between the first and second administrations in phase III trials was 42-45 weeks.³</td>
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A recent Cochrane review noted that although the pool of randomised data is still small, it does support the efficacy of BTX-A in the treatment of OAB, though due to the limited data, the issues of long term safety, optimal dose, and best injection technique remain largely unanswered. It highlighted that botulinum toxin may result in the need to initiate CIC, thus patients need to be counselled about this risk and those unwilling to undertake CIC under any circumstances should not be a candidate for botulinum toxin therapy.\textsuperscript{1}

There is now further support in the literature for the efficacy of BTX-A in the form of two large, randomised, double blind placebo-controlled trials which supported the licensing of Botox for the treatment of urinary incontinence due to neurogenic detrusor overactivity.\textsuperscript{4,5} They recruited 691 patients with spinal cord injury (SCI) or MS who had an inadequate response to or were intolerant of at least one anticholinergic medication. Both studies showed statistically significant decreases in the primary efficacy measure of weekly frequency of incontinence episodes in the Botox group compared with placebo (in both studies, mean $\downarrow$ of $\sim$22 episodes across both dose groups vs. mean $\downarrow$ of 11 for placebo group), as well as improved urodynamics and QOL. The most common adverse reactions observed more frequently following injection of Botox were urinary tract infection (UTI) and urinary retention. Those who developed urinary retention after Botox may require self-catheterisation to empty the bladder.\textsuperscript{4-6}

A large trial of BTX-A for refractory detrusor overactivity in women (n=240) conducted in eight UK urogynaecology centres reported a lower voiding frequency with BTX compared with placebo at 6 months. (8.3 vs. 9.67 per 24 hours; p=0.0001) and similarly in urgency and leakage episodes. Continence was more common after BTX-A (31% vs 12%). UTI and voiding difficulty requiring self-catheterisation were more common after BTX-A.\textsuperscript{7}

In a RCT comparing anticholinergic therapy and onabotulinumtoxinA injection in the treatment of urgency urinary incontinence in 249 women, both treatments were associated with similar reductions in the frequency of daily episodes of urgency urinary incontinence, but the onabotulinumtoxinA group was less likely to have dry mouth and more likely to have complete resolution of urgency urinary incontinence as well as higher rates of transient urinary retention and UTIs.\textsuperscript{8}

A British economic study funded by the MS Society and Pfizer Inc, assessed the resource utilisation, health benefits and cost-effectiveness of intra-detrusor injections of BTX-A in patients with overactive bladder and concluded that it was likely to be a cost-effective intervention from the perspective of the NHS.\textsuperscript{9,10}

NICE has issued several pieces of guidance on the management of urinary incontinence, supporting the use of BTX-A in the following settings, providing patients are willing and able to self-catheterise, whilst acknowledging that two of the uses* are outside the UK marketing authorisation for the product and thus informed consent to treatment should be obtained and documented:

- Treatment of adults with spinal cord disease and with symptoms of an overactive bladder OR with urodynamic investigations showing...
impaired bladder storage, in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.¹¹
- Treatment of idiopathic detrusor overactivity in women who have not responded to conservative treatments.¹²
- Treatment of detrusor overactivity in men whose symptoms have not responded to conservative management and drug treatments.¹³

Recent European¹⁴,¹⁵ and US guidance¹⁶ also supports the use of botulinum toxin A intravesical injections in patients with urgency urinary incontinence refractory to antimuscarinic therapy.

At present, BTX-A is only licensed for the treatment of urinary incontinence due to detrusor overactivity associated with a neurological condition. It is not known if there are plans to extend the license to include other types of incontinence. There is a large body of published evidence on the use of Botox for urinary incontinence, much of which come from small short term studies, though more recently, some larger RCTs in neurogenic OAB, detrusor overactivity and urgency urinary incontinence, have been published, supporting efficacy of this intervention. However, issues of long term safety, optimal dose, and best injection technique require further investigation. The main trials have involved more women than men. In the studies that have included both genders, no subgroup analyses according to gender were conducted and there is nothing in the published literature to suggest variation in response between these groups.

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<th>The intervention</th>
<th>Mechanism of action</th>
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<td>Botulinum toxin is an acetylcholine release inhibitor and a neuromuscular blocking agent¹⁷ that is postulated to work in OAB via several separate mechanisms but its exact action is not completely understood. It is injected via cystoscopy into the detrusor at multiple sites,¹ and treatment results in relaxation of the bladder, an increase in its storage capacity and a decrease in urinary incontinence.¹⁵</td>
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<th>Licensed indication</th>
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<td>There is only one botulinum toxin preparation licensed for urological use: Botox® (onabotulinumtoxinA) received a marketing authorisation in September 2012 for the management of urinary incontinence in adult patients with neurogenic detrusor overactivity due to subcervical spinal cord injury (traumatic or non-traumatic) or multiple sclerosis, who are not adequately managed with anticholinergics; patients should be already catheterising or willing and able to catheterise if required.³</td>
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<th>Usual dosage</th>
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<td>The licensed dose of Botox® is 200 Units as 1 ml (~6.7 Units) injections across 30 sites in the detrusor muscle.³</td>
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<th>Treatment alternatives/ place in therapy</th>
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<td>First line treatment consists of behavioural and lifestyle modifications which may be supplemented with antimuscarinic drugs, and in some cases, CIC. Antimuscarinic drugs can improve symptoms but are often poorly tolerated, and often cause patients to discontinue treatment. More invasive treatment options used as second or third line treatments include pudendal or sacral nerve stimulation, augmentation cystoplasty, bladder instillation of vanilloids (resiniferatoxin).⁵</td>
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<th>Future alternatives</th>
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### National guidance

NICE has issued several pieces of guidance on the management of urinary incontinence, which addresses the use of BTX-A, though at the time of the guidance, it was noted that BTX-A had been rapidly adopted in clinical practice in advance of high-quality data on efficacy, safety and long-term outcomes.

The guidance contains the following recommendations:

**Urinary incontinence in neurological disease (CG 148 issued August 2012)**

Offer bladder wall injection with BTX-A to adults with spinal cord disease (e.g. SCI or MS) and with symptoms of an overactive bladder or with urodynamic investigations showing impaired bladder storage, and in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

- Ensure that patients who have been offered continuing treatment with repeated BTX-A injections have prompt access to repeat injections when symptoms return.
- Before offering bladder wall injection with BTX-A: explain to the person and/or their family members and carers that a catheterisation regimen is needed in most people with neurogenic lower urinary tract dysfunction after treatment, and ensure that they are able and willing to manage such a regimen should urinary retention develop after the treatment.

**Urinary incontinence in women (CG 40 issued 2006)**

Bladder wall injection with BTX-A should be used in the treatment of idiopathic detrusor overactivity only in women who have not responded to conservative treatments, and who are willing and able to self-catheterise. Women should be informed about the lack of long-term data. There should be special arrangements for audit or research.

**Lower urinary tract symptoms in men (CG 97 issued 2010)**

Consideration should be given to offering bladder wall injection with BTX-A to men with detrusor overactivity only if their symptoms have not responded to conservative management and drug treatments and the man is willing and able to self-catheterise.

### Evidence for use

A recent Cochrane review has evaluated the literature on the safety, optimal dose, injection technique and efficacy of intravesical botulinum toxin injection for neurogenic and idiopathic OAB in adults with or without incontinence.

A literature search was conducted on 23 February 2010 for all randomised or quasi-randomised controlled trials, in which at least one management arm involved botulinum toxin. Comparison interventions could include no intervention, placebo, lifestyle modification, bladder retraining, pharmacological treatments, surgery, bladder instillation techniques, neuromodulation, and different types, doses, and injection techniques of botulinum toxin. Overall 19 studies were identified, published up to 2009, of which 9 were only available as abstracts at that time.

Ten of the included studies compared botulinum toxin with placebo, two
of which used BTX type B and the other eight studies used type A. The studies were small, ranging from 14 to 77 participants with an average of 37 participants. The majority of the studies were double blinded and all were randomised. The majority of included studies involved participants with neurogenic OAB, often due to SCI or MS. Seven studies included only participants with idiopathic OAB. The majority of participants had symptoms refractory to antimuscarinics or did not tolerate the medication as an inclusion criteria. The studies varied in whether or not participants were allowed to continue antimuscarinic medications for OAB during the follow up period. Where stated, participants were of mixed gender except in two studies with women only. Details of the participants’ demographics were often poorly documented in the studies. All studies followed participants after a single dose of BTX, except one where the participants were re-injected every six months and one where the participants were offered open label use of botulinum toxin at 36 weeks. The length of predetermined follow up varied from six weeks to 24 months.¹

Little data could be synthesised across studies due to differing study designs and outcome measures. The review found that:

- All studies demonstrated superiority of botulinum toxin to placebo.
- A significant clinical response may be seen in up to 60 to 90% of patients.
- Of patients with OAB with incontinence, up to 66% may achieve complete continence.
- Benefits may be seen for between 3 and 12 months and is dependent upon dose and type of toxin used.
- Lower doses of botulinum toxin (100 to 150 U) appeared to have beneficial effects, but larger doses (300 U) may have been more effective and longer lasting, but with more side effects.
- There are consistent improvements in urodynamic parameters (maximum cystometric capacity [MCC] and maximum detrusor pressure [MDP]) with botulinum toxin.

Intravesical botulinum toxin was considered to be reasonably safe based on these data; however, one study was halted due to a perceived unacceptable rate of urinary retention. Botulinum toxin causes an increase in post-void residual urine volume (PVR) in up to 72% of patients, which in many cases was clinically significant, but may necessitate the commencement of CIC in some patients. UTI rates reported were considered consistently comparable to that related to cystoscopy alone. Other adverse events were uncommon in the included studies however they included small numbers of participants and may have been underpowered to detect rare adverse events.¹

The review concluded that although the pool of randomised data is still small, with the largest study examining 77 patients, they support the efficacy of botulinum toxin in the treatment of OAB. Due to the limited body of data, the issues of long term safety, optimal dose, and best
injection technique remain largely unanswered. In addition, it was noted that as the data presented are based on patient groups with severe, otherwise treatment refractory OAB, caution should be exercised in treating patients with milder symptoms, or those who have not exhausted conventional treatment options. Furthermore, patients have an overall improvement in urinary symptom score after botulinum toxin even when it results in the need to initiate CIC, thus adequate counselling about the risk of requiring CIC should be mandatory, and a patient who is unwilling to undertake CIC under any circumstances should not be a candidate for botulinum toxin therapy. It was not possible to draw conclusions about non-neurogenic incontinence from this review.

In a systematic review, Mangera et al. compare the reported outcomes of Botox (onabotulinumtoxinA) and Dysport (abobotulinumtoxinA) in the treatment of the following disorders of the lower urinary tract: neurogenic detrusor overactivity (NDO), idiopathic detrusor overactivity (IDO), painful bladder syndrome (PBS), and lower urinary tract symptoms resulting from bladder outflow obstruction (BOO) or detrusor sphincter dyssynergia (DSD). When considering all studies, onabotulinumtoxinA was better studied than abobotulinumtoxinA. The following findings were noted:

- High-level data show the benefits of both onabotulinumtoxinA and abobotulinumtoxinA in the treatment of NDO in adults.
- High-level data support the use of onabotulinumtoxinA for IDO in adults.
- Only onabotulinumtoxinA has been described in high level studies in adults with BOO although the literature is still poor in this area.
- Only onabotulinumtoxinA has level 1 evidence supporting its use in adults with DSD, although the literature is still poor in this area.
- Only onabotulinumtoxinA has been used in patients with PBS/IC in both high- and low-level studies, but the literature is still poor in this area.

Both of these systematic reviews also showed that the number of injection sites varied from 3 to 40, with 20 being most common, and the injection volume ranged between 3 and 30 mL, with 20 mL being the most common. The choice of injection site did not seem to impact on efficacy or adverse events. A range of 27-43% of patients had a PVR > 200 mL, while 13-44% suffered from UTI.

Since the publication of the reviews which noted the limited controlled trial data on benefits and safety compared with other interventions, or with placebo, the two studies supporting the regulatory approval of Botox for the treatment of urinary incontinence due to neurogenic detrusor overactivity have been published. These were large, randomised, double blind placebo-controlled multicentre trials (Cruz 2011, Ginseng 2012), which formed part of the DIGNITY (Double-Blind Investigation of Purified Neurotoxin Complex in Neurogenic Detrusor...
Overactivity) Study programme. They recruited 691 SCI (T1 or below) or MS patients (291 men, 400 women), who were either spontaneously voiding or using catheterisation and who had an inadequate response to or were intolerant of at least one anticholinergic medication. They were randomised to receive either 200 Units of Botox (n=227), 300 Units of Botox (n=223), or placebo (n=241). One repeat treatment could be requested from 12 weeks onwards after the first treatment. To qualify for repeat treatment, patients had to have <30% (or < 50% Ginsberg study) reduction from baseline in weekly urinary incontinence (UI) episodes. Patients initially assigned to placebo received Botox 200 U or 300 U at retreatment according to a preassigned sequence.4-6

The study drug was administered via cystoscopy as 30 intradetrusor injections (1 ml each) approximately 1 cm apart and to a depth of 2 mm, sparing the trigone. Study visits occurred at weeks 2, 6, and 12 after treatment and every 6 weeks thereafter until re-treatment or study exit. Patients used a 7-day bladder diary before the baseline and each follow-up visit. Urodynamic assessments were performed at baseline and 6 weeks posttreatment.4-6

The primary end point was change from baseline in UI episodes per week (week 6). Secondary end points included urodynamics (maximum cystometric capacity [MCC], maximum detrusor pressure during first involuntary detrusor contraction (DP), and Incontinence Quality of Life (I-QOL) total score.4-6

- At baseline, mean UI episodes per week (~33) were similar across groups. In both studies, statistically significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes at week 6 were observed for Botox 200 U and 300 U [-21.8 and -19.4, respectively compared with -13.2 in the placebo group (p < 0.01) in Cruz’s study4 and -21 and -23 episodes, respectively, vs. 9 placebo (each dose p <0.001) in Ginsberg’s study5].

- During week 6, 36-41% of patients in the onabotulinumtoxinA groups compared with up to 10% of patients on placebo were fully continent (“dry”).

- Improvements in MCC, DP and I-QOL at week 6 were statistically significantly greater with both Botox doses than with placebo (p<0.001).

- The median time to patient request for retreatment was in the range 254 to 294 days for the Botox groups in both studies and greater than placebo (~92 days, p<0.001).

- There was a higher incidence of adverse events (AEs) in the Botox groups (~ 70%) compared with placebo group (~56%). The most frequent AEs were localised urological events (UTIs and urinary retention [UR]) which occurred more often in the Botox group: UTI in 18-22% on placebo vs. 28% on 200 U and 28-38% on 300 U, UR in 3% on placebo, 20% on 200 U and 17-31% on 300 U.
Significant increases in PVR were observed in patients not using CIC prior to treatment, and 10-12%, 30-35%, and 42% of patients in the placebo, 200 U, and 300 U groups, respectively, initiated CIC post-treatment due to UR.

These studies demonstrated a statistically significantly reduced UI and improved urodynamics and QOL in MS and SCI patients with NDO treated with Botox compared to placebo, though the former was linked to a higher incidence of adverse effects, and CIC initiation due to UR appeared to increase in a dose dependent fashion. Both doses were well tolerated with no clinically relevant differences in efficacy or duration of effect between them.4-6

A recent study evaluated the efficacy and safety of Botox for the treatment of detrusor overactivity (DO) in women. The double-blind placebo-controlled randomised trial was conducted in 8 UK urogynaecology centres between 2006 and 2009 and involved 240 women with refractory disease. They were randomised to receive 200 U Botox (n= 122) or placebo (n= 118) injected into the bladder wall (20 sites; 10 U per site in 1ml saline). The primary outcome was voiding frequency per 24 hours at 6 months. Secondary outcomes included urgency and incontinence episodes and QOL data.7

The following findings were reported:

- Median voiding frequency was lower after Botox compared with placebo (8.3 vs. 9.67, difference: 1.34; p=0.0001).
- Similar differences were seen in urgency episodes (3.83 vs. 6.33, difference: 2.50; p<0.0001) and leakage episodes (1.67 vs. 6.0; difference: 4.33; p<0.0001).
- Continence was more common after Botox (31% vs 12%; odds ratio [OR]: 3.12; 95% CI, 1.49-6.52; p=0.002).
- UTI (31% vs. 11%; OR: 3.68; 95% CI, 1.72-8.25; p=0.0003) and voiding difficulty requiring self-catheterisation (16% vs. 4%; OR: 4.87; 95% CI, 1.52-20.33; p=0.003) were more common after Botox.

This study of refractory DO in women confirms the short term efficacy of Botox though UTI and self-catheterisation were more common with its use.7

Anticholinergic medications and Botox A have been compared in a recent double-blind, placebo–controlled, randomised study of urgency urinary incontinence in women, who had ≥5 episodes of incontinence per 3-day period. They were randomised for a 6-month period to daily oral anticholinergic medication (solifenacin, 5mg initially, with possible escalation to 10mg and, if necessary, subsequent switch to trospium XR, 60mg) plus one intradetrusor injection of saline or one intradetrusor injection of 100U of onabotulinumtoxinA plus daily oral placebo. The primary outcome was the reduction from baseline in mean episodes of urgency urinary incontinence per day over the 6-month period, as
recorded in 3-day diaries submitted monthly. Secondary outcomes included complete resolution of urgency urinary incontinence, quality of life, use of catheters, and adverse events. Of 249 women who underwent randomisation, 247 were treated, and 241 had data available for the primary outcome analyses. The following data were reported:

- The mean reduction in episodes of urgency urinary incontinence per day over the course of 6 months, from a baseline average of 5.0 per day, was 3.4 in the anticholinergic group and 3.3 in the onabotulinumtoxinA group (p=0.81).

- Complete resolution of urgency urinary incontinence was reported by 13% and 27% of the women, respectively (p=0.003).

- Quality of life improved in both groups, without significant between-group differences.

- The anticholinergic group had a higher rate of dry mouth (46% vs. 31%, p=0.02) but lower rates of catheter use at 2 months (0% vs. 5%, p=0.01) and UTIs (13% vs. 33%, p<0.001).

This study concluded that anticholinergic therapy and onabotulinumtoxinA injection were associated with similar reductions in the frequency of daily episodes of urgency urinary incontinence, but the onabotulinumtoxinA group was less likely to have dry mouth and more likely to have complete resolution of urgency urinary incontinence as well as higher rates of transient urinary retention and UTIs.

### Safety

The studies in the DIGNITY Study program reported a higher incidence of adverse events (AEs) in the Botox groups (~70%) compared with placebo (~56%). The most frequent AEs were localised urological events (UTIs and urinary retention [UR]) which occurred more often in the Botox group: UTI in 18-22% on placebo vs. 28% on 200 U and 28-38% on 300 units, UR in 3% on placebo, 20% on 200 U and 17-31% on 300 U. Significant increases in post-void residual were observed in patients not using CIC prior to treatment, and 10-12%, 30-35%, and 42% of patients in the placebo, 200-U, and 300-U groups, respectively, initiated CIC post-treatment due to UR. Tinchello et al also reported a higher incidence of UTI (31% vs. 11%) and voiding difficulty requiring self-catheterisation (16% vs. 4%) in the Botox group compared with placebo. The Cochrane review noted that as botulinum toxin can result in the need to initiate CIC, adequate counselling about this risk should be mandatory, and a patient who is unwilling to undertake CIC under any circumstances should not be a candidate for botulinum toxin therapy. In Visco et al’s trial comparing BTX-A with anticholinergic therapy, the latter group had a higher rate of dry mouth (46% vs. 31%) but lower rates of catheter use at 2 months (0% vs. 5%) and UTIs (13% vs. 33%).

### Costs

- **Tariff status**

- **Activity costs**

The NHS list price of the licensed dose of Botox 200 Units is £276.40 and based on the median interval between the first and second administrations in phase III trials, patient could receive a second injection within the same year which equates to annual drug cost of ~
Costs of alternatives

Cost effectiveness (if available)

A British economic study (2006) funded by the MS Society and Pfizer Inc, aimed to assess the resource utilisation, health benefits and cost-effectiveness of intra-detrusor injections of Botox in patients with OAB. Data were analysed on 101 patients with OAB of either neurogenic (NDO; n = 63) or idiopathic (IDO; n = 38) origin who received intra-detrusor injections of 200-300 units in 20-30 ml saline as part of a research protocol. Twenty-nine patients received repeat injections after 7 to 26 months. Symptom severity and urodynamic parameters were assessed at 0, 4 and 16 weeks.\textsuperscript{12,13}

The analysis of costs was conducted from the perspective of the NHS. The categories of costs included were pre-operation, intra-operation and post-operation. Pre-operation included consultant, cystometry or urodynamics, and urinalysis. Intra-operation included Botox, saline, needle, saline irrigation, theatre cost and antibiotic prophylaxis. Post-operation included specialist registrar, specialist urology nurse and urinalysis. Statistical analyses of the costs were not carried out.\textsuperscript{12,13}

A clinical improvement was defined as an improvement of at least 25% in at least two out of five key parameters. Specifically, micturition episodes per 24 hours ("frequency"), number of voids associated with urgency per 24 hours ("urgency"), number of urgency incontinence events per 24 hours ("leakage"), maximum cyctometric capacity (MCC) and maximum detrusor pressure (MDP/ Pdetmax). Symptoms were recorded on a voiding diary. In addition to the 25% definition of clinical improvement, a secondary analysis considered a 50% definition.\textsuperscript{12,13}

In an intent-to-treat analysis:

- 82% of patients showed a 25% or greater improvement in at least 2 out of 5 parameters (urinary frequency, urgency, urinary incontinence (UI) episodes, MCC, and MDP) 4 weeks after treatment, reducing to 65% after 16 weeks.

- A 50% or greater improvement in the frequency of micturition, urgency or urinary incontinence was seen in 73% of patients at 4 weeks and 54% at 16 weeks.

- There were no significant differences between IDO and NDO patients in the proportion meeting these endpoints.

The following costs were calculated:

- The cost of administering one set of Botox injections was £826 (£745.33 for the typical IDO patient and £874.62 for the typical NDO patient).

- The cost per treated year (cost per time to re-injection) was £507 (£386 for the typical IDO patient and £609 for the typical NDO patient).
The cost per improved patient per year was £617 (£480 for the typical IDO patient and £745 for the typical NDO patient) when using the 25% definition, and £715 (£510 for the typical IDO patient and £928 for the typical NDO patient) when using the 50% definition.

The cost per initial response was £1005 (£944 for the typical IDO patient and £1040 for the typical NDO patient) when using the 25% definition, and £1127 (£1089 for the typical IDO patient and £1148 for the typical NDO patient) when using the 50% definition.

The cost per sustained response was £1264 (£1416 for the typical IDO patient and £1198 for the typical NDO patient) when using the 25% definition, and £1545 (£1770 for the typical IDO patient and £1450 for the typical NDO patient) when using the 50% definition.

The sensitivity analysis showed that the cost-effectiveness ratios increased by 14 to 16% when the injection time was doubled, and decreased by 15 to 17% when excluding the costs of urodynamics and urinalysis.

This study concluded that Botox injection was an effective treatment for patients with urodynamically-proven detrusor overactivity of either neurogenic or idiopathic origin, and was likely to be a cost-effective intervention from the perspective of the NHS.\textsuperscript{12,13}

| Potential number of patients in Bedfordshire and Luton | OAB is estimated to affect approximately 10.9% of men and 12.9% women, with up to 28% of these men and 48% of these women reporting symptoms of incontinence.\textsuperscript{1} |
| Impact per 100,000 population | One British study has estimated that the overall prevalence of OAB-related symptoms was 3.87 per 1000 persons, with an incidence of 2.79 per 1000 person-years.\textsuperscript{19} |
| Affordability considerations |  |

| Number Needed to Treat (NNT) |  |
| Number Needed to Harm (NNH) |  |

| Ethics |  |
| Equity |  |
| Implementation |  |

| Patient choice/access considerations |  |
European Association of Urology (EAU) 2012 guidelines on urinary incontinence has reviewed the evidence and concluded the following about the data (see appendix for key to evidence classification):¹⁴

- A single treatment session of intravesical onabotulinumtoxinA (100-300 U) is more effective than placebo at curing and improving urgency urinary incontinence for up to 12 months. ¹ᵃ
- There is no evidence that repeated injections of botulinum toxin A have reduced efficacy. ³
- There is a high risk of increased post-void residual (PVR), which is dose dependent and may require intermittent self-catheterisation. ¹ᵇ
- There is a high risk of UTI in those who require intermittent self-catheterisation. ¹ᵇ
- There is no evidence that one technique of injecting botulinum toxin A is more efficacious than another. ¹ᵇ

This led to the following recommendations:¹⁴

- Offer botulinum toxin A intravesical injections to patients with urgency urinary incontinence refractory to antimuscarinic therapy. ³
- Warn patients of the possible need to self-catheterise and the associated risk of urinary tract infection; ensure that they are willing and able to do so. ³
- Patients should also be warned of the licensing status of botulinum toxin A, and that the long-term effects remain unknown. ³

The EAU also issued guidelines on the management of neurogenic lower urinary tract dysfunction in 2012 which noted that botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity (level A). An injection causes a long-lasting but reversible chemical denervation that lasts for about 9 months. Generalised muscular weakness is an occasional adverse effect. Histological studies have not found ultrastructural changes after injection.¹⁵

According to 2012 guidelines from the American Urological Association Education and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction on the diagnosis and treatment of non-neurogenic OAB, third line treatment options include onabotulinumtoxinA therapy for carefully selected patients who have failed behavioural and anti-muscarinic therapy or who are not candidates for these therapies and continue to have bothersome symptoms after appropriate counselling (evidence strength: Grade C). The patient must be able and willing to return for frequent PVR evaluation and able and willing to perform self-catheterisation if necessary. However, the use of onabotulinumtoxinA in non-neurogenic OAB patients is not licensed. It is noted that reductions in frequency, nocturia, pad use and incontinence, improvement in urodynamics parameters and improvement in QoL measures diminish over time requiring repeat injections to restore improvements. In addition, substantial rates of adverse events occurred in the active treatment groups.¹⁶
At present, there is only one botulinum toxin preparation licensed for urological use: Botox® (onabotulinumtoxinA) received a marketing authorisation in September 2012 for the treatment of urinary incontinence due to detrusor overactivity associated with a neurological condition. It is not known if there are plans to extend the license to include other types of incontinence. There is a large body of published evidence on the use of Botox for urinary incontinence, much of which come from small short term studies, though more recently, some larger RCTs in neurogenic OAB, detrusor overactivity and urgency urinary incontinence have been published, supporting efficacy of this intervention. However, issues of long term safety, optimal dose, and best injection technique require further investigation, as does the effects of repeat injection. It should noted be that use of BTX-A is linked to an increase in PVR that may require need for CIC which in turn is associated with an increased risk of UTIs.

<table>
<thead>
<tr>
<th>Points for consideration</th>
<th>Limitations of review</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

Options for JPC

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


3. Allergan Ltd. BOTOX 50, 100, 200 Units. Link to 100 unit SPC (DOR 24/09/2012). [http://www.medicines.org.uk/EMC/medicine/22562/SPC/Botox+200+Units/#INDICATIONS](http://www.medicines.org.uk/EMC/medicine/22562/SPC/Botox+200+Units/#INDICATIONS)


10. Centre for Reviews and Dissemination. Review of cost-consequence analysis (Kalsi V) accession number 22006000415. [http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=22006000415](http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=22006000415)


http://guidance.nice.org.uk/CG97/Guidance/pdf/English

European Association of Urology 2012.  
http://www.uroweb.org/gls/pdf/18_Urinary_Incontinence_LR_1%20Octob er%202012.pdf

http://www.uroweb.org/gls/pdf/19_Neurogenic_LR%20II.pdf


17. FDA. FDA approves Botox to treat specific form of urinary incontinence.  
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm269509.htm

18. MIMS November 2012

Appendix: grades of evidence and recommendations

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a:</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b:</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a:</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b:</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3:</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4:</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nature of recommendations</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>A:</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B:</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C:</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
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</table>
**Treatment assessed: Botulinum toxin for overactive bladder (December 2012)**

**JPC Recommendation:**
The Committee agreed to support the use of Botulinum A (Onabotulinum toxinA) to treat over active bladder in men and women in accordance with NICE Clinical Guidelines (CG 148, issued August 2012, CG 40, issued 2006 and CG 97, issued 2010):

<table>
<thead>
<tr>
<th>Urinary incontinence in neurological disease (CG 148 issued August 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer bladder wall injection with BTX-A to adults with spinal cord disease (e.g. SCI or MS) and with symptoms of an overactive bladder or with urodynamic investigations showing impaired bladder storage, and in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.</td>
</tr>
</tbody>
</table>

- Ensure that patients who have been offered continuing treatment with repeated BTX-A injections have prompt access to repeat injections when symptoms return.

- Before offering bladder wall injection with BTX-A: explain to the person and/or their family members and carers that a catheterisation regimen is needed in most people with neurogenic lower urinary tract dysfunction after treatment, and ensure that they are able and willing to manage such a regimen should urinary retention develop after the treatment.

<table>
<thead>
<tr>
<th>Urinary incontinence in women (CG 40 issued 2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder wall injection with BTX-A should be used in the treatment of idiopathic detrusor overactivity only in women who have not responded to conservative treatments, and who are willing and able to self-catheterise. Women should be informed about the lack of long-term data. There should be special arrangements for audit or research.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lower urinary tract symptoms in men (CG 97 issued 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consideration should be given to offering bladder wall injection with BTX-A to men with detrusor overactivity only if their symptoms have not responded to conservative management and drug treatments and the man is willing and able to self-catheterise.</td>
</tr>
</tbody>
</table>

1) **Clinical Effectiveness**

A recent Cochrane review noted that although the pool of randomised data is still small, it does support the efficacy of botulinum toxin A in the treatment of OAB, though due to the limited data, the issues of long term safety, optimal dose, and best injection technique remain largely unanswered. It highlighted that botulinum toxin may result in the need to initiate clean intermittent catheterisation (CIC), thus patients need to be counselled about this risk and those unwilling to undertake CIC under any circumstances should not be a candidate for botulinum toxin therapy.

There is now further support in the literature for the efficacy of botulinum toxin in the form of two large, randomised, double blind placebo-controlled trials which supported the licensing of Botox for the treatment of urinary incontinence due to neurogenic detrusor overactivity. They recruited 691 patients with spinal cord injury or MS who had an inadequate response to or were intolerant of at least one anticholinergic medication. Both studies showed statistically significant decreases in the primary efficacy measure of weekly frequency of incontinence episodes in the Botox group.
compared with placebo (in both studies, mean ↓ of ~22 episodes across both dose groups vs. mean ↓ of 11 for placebo group), as well as improved urodynamics and QOL. The most common adverse reactions observed more frequently following injection of Botox were UTI and urinary retention. Those who developed urinary retention after Botox may require self-catheterisation to empty the bladder.

A trial of BTX for refractory detrusor overactivity in women (n= 240) conducted in eight UK urogynaecology centres reported a lower voiding frequency with BTX compared with placebo at 6 months. (8.3 vs. 9.67 per 24 hours; p=0.0001) and similarly in urgency and leakage episodes. Continence was more common after BTX (31% vs 12%). UTI and voiding difficulty requiring self-catheterisation were more common after BTX.

In a RCT comparing anticholinergic therapy and onabotulinumtoxinA injection in the treatment of urgency urinary incontinence in 249 women, both treatments were associated with similar reductions in the frequency of daily episodes of urgency urinary incontinence, but the onabotulinumtoxinA group was less likely to have dry mouth and more likely to have complete resolution of urgency urinary incontinence as well as higher rates of transient urinary retention and UTIs.

NICE guidance and recent European and US guidelines support the use of botulinum toxin A in patients with OAB who have not responded to conservative treatments, and who are willing and able to self catheterise.

The main trials have involved more women than men. In the studies that have included both genders, no subgroup analyses according to gender were conducted and there is nothing in the published literature to suggest variation in response between these groups.

2) **Cost**
The cost of the licensed dose of 200 Units is £276.40\(^{13}\) and based on the median interval between the first and second administrations reported in phase III trials, patient could receive a second injection within the same year which equates to annual drug cost of ~ £550.

3) **Equity**
No issues identified.

4) **Needs of the community**
OAB is estimated to affect approximately 10.9% of men and 12.9% women, with up to 28% of these men and 48% of these women reporting symptoms of incontinence. One British study has estimated that the overall prevalence of OAB-related symptoms was 3.87 per 1000 persons, with an incidence of 2.79 per 1000 person-years.

5) **Need for healthcare (incorporates patient choice and exceptional need)**
Other treatment options are available but tend to be more invasive.

6) **Policy drivers**
NICE Clinical Guidelines (CG 148, issued August 2012; CG 40, issued 2006; CG 97 issued 2010)

7) **Disinvestment**
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

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

* 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.


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

Linating Centre for the Adoption of Evidence Based practice and innovation