botulinum toxin type A 50, 100, 200 Allergan units/vial (Botox®)
SMC No. (916/13)

Allergan Ltd
06 September 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

*botulinum toxin type A (Botox®)* is accepted for use within NHS Scotland.

**Indication under review**: 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.

In two phase III, double-blind, placebo-controlled studies, in which all patients received best supportive care, botulinum toxin type A 200 units (licensed dose) was significantly superior to placebo for mean reduction in weekly urinary incontinence episodes, from baseline to week six. There are currently limited data on re-treatment.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
Indication
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.

Dosing Information
Botulinum toxin type A should only be given by physicians with appropriate qualifications, and expertise in the treatment and the use of the required equipment.

Botulinum toxin type A (Botox®) 200 units, as 1mL (~6.7 units) injections across 30 sites in the detrusor muscle.
[See summary of product characteristics for further detail.]

Re-treatment
Patients should be considered for re-injection when the clinical effect of the previous injection has diminished, but no sooner than three months from the prior bladder injection. In phase 3 clinical studies, the median interval between the first and second administrations was 42 weeks in patients with spinal cord injury and 45 weeks in patients with multiple sclerosis.

Limited data are available beyond two treatments. No urodynamic data beyond two treatments and no histopathological data after repeated treatment are currently available.

Patients should not receive multiple treatments in the event of limited symptomatic improvement.

Product availability date
1 October 2012

Summary of evidence on comparative efficacy
Botox® is the first botulinum toxin type A preparation licensed for use in urinary incontinence in patients with neurogenic detrusor overactivity due to subcervical spinal cord injury (SCI) or multiple sclerosis (MS). Botulinum toxin blocks acetylcholine release pre-synaptically, resulting in paralysis of the detrusor smooth muscle, and also modulates intrinsic bladder reflexes.¹ Patients with SCI or MS often have neurogenic detrusor overactivity and management initially is with anticholinergics and clean intermittent catheterisation.²

Two similarly designed phase III, double-blind, placebo-controlled studies (study 515 and study 516) have been conducted in patients aged 18 to 80 years with neurogenic detrusor overactivity (for at least three months) secondary to SCI (T1 or below) or MS (with an expanded disability status score [EDSS] ≤6.5).¹⁻³ Patients were required to have ≥14 urinary incontinence episodes per week and be inadequately controlled on anticholinergics (in the opinion of the investigator). Neurogenic detrusor overactivity was demonstrated by involuntary detrusor contraction (IDC) during bladder filling. Patients who were not performing clean intermittent catheterisation at baseline had to be willing to initiate it, if needed.
Patients were randomised equally (stratified by centre according to aetiology and anticholinergic use) to botulinum toxin type A 200 units, 300 units or placebo in addition to best supportive care (BSC). BSC included behavioural therapy and incontinence pads alone or in combination with anticholinergics and/or clean intermittent catheterisation. Patients were not permitted to start anticholinergics during the study and anticholinergics taken at baseline were to be continued at a stable dose. Botulinum toxin type A was administered (with no anaesthesia, local anaesthesia with/without sedation or general anaesthesia) as 30 injections of 1mL about 1cm apart and 2mm deep in the detrusor muscle, sparing the trigone. Patients could receive a second treatment following fulfilment of pre-defined re-treatment criteria: patient initiated request; <50% reduction from baseline in frequency of urinary incontinence episodes in study 515 and <30% in study 516; and ≥12 weeks since previous treatment. For the second treatment, patients initially assigned to placebo received botulinum toxin type A 200 units or 300 units according to a pre-assigned sequence. Patients were followed up for a maximum of 64 weeks.

Results for botulinum toxin type A 200 units (licensed dose) and placebo only are reported below. Botulinum toxin type A 200 units was significantly superior to placebo for the primary endpoint of mean change in mean weekly urinary incontinence episodes from baseline to week six. The proportion of responders (≥50% decrease and 100% decrease in weekly urinary incontinence episodes from baseline to week six) was also analysed. Secondary endpoints included change in maximum cystometric capacity and change in maximum detrusor pressure at first IDC. Quality of life was measured using the validated incontinence-quality of life (I-QOL) questionnaire with total score range: 0 (maximum problem) to 100 (no problem at all). The primary (≥8 point increase from baseline) and secondary (≥11 point increase) definitions of responders were pre-defined and considered clinically relevant. There were significant results for botulinum toxin type A 200 units versus placebo for all secondary endpoints. Results of the primary and some secondary endpoints are included in the table below.

Table: primary and key secondary endpoints for studies 515 and 516 1-3

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Study 515</th>
<th>Study 516</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Botulinum toxin type A 200</td>
<td>Botulinum toxin type A 200</td>
</tr>
<tr>
<td></td>
<td>units N=135</td>
<td>units N=92</td>
</tr>
<tr>
<td></td>
<td>Placebo N=149</td>
<td>Placebo N=92</td>
</tr>
<tr>
<td>Baseline</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Mean change at week 6 (SD)</td>
<td>-21.0 (23.8)</td>
<td>-8.8 (16.2)</td>
</tr>
<tr>
<td>≥50% decrease from baseline in weekly urinary incontinence episodes responder</td>
<td>75%</td>
<td>38%</td>
</tr>
<tr>
<td>Responder, %</td>
<td>36%</td>
<td>10%</td>
</tr>
<tr>
<td>100% decrease from baseline in weekly urinary incontinence episodes responder</td>
<td>38%</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

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Table: primary and key secondary endpoints for studies 515 and 516 1-3

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<tr>
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<th>Study 515</th>
<th>Study 516</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Botulinum toxin type A 200</td>
<td>Botulinum toxin type A 200</td>
</tr>
<tr>
<td></td>
<td>units N=135</td>
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<td>Placebo N=149</td>
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<td>Baseline</td>
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<td>7.6%</td>
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<tr>
<td>Endpoints</td>
<td>Study 515</td>
<td>Study 516</td>
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<tr>
<td>-----------</td>
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<td>-----------</td>
</tr>
<tr>
<td>Botulinum toxin type A 200 units N=135</td>
<td>Placebo N=149</td>
<td>Botulinum toxin type A 200 units N=92</td>
</tr>
</tbody>
</table>

**Secondary endpoints (selected)**

**Bladder capacity; maximum cystometric capacity**

<table>
<thead>
<tr>
<th>Baseline, mL</th>
<th>Mean change at week 6, mL</th>
</tr>
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<tbody>
<tr>
<td>252mL</td>
<td>+151mL</td>
</tr>
<tr>
<td>256mL</td>
<td>+16mL</td>
</tr>
<tr>
<td>247mL</td>
<td>+157mL</td>
</tr>
<tr>
<td>249mL</td>
<td>+6.5mL</td>
</tr>
</tbody>
</table>

**Bladder Pressure; maximum detrusor pressure at first IDC**

<table>
<thead>
<tr>
<th>Baseline, cm H2O</th>
<th>Mean change at week 6, cm H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>51.3 cm H2O</td>
<td>-35.1 cm H2O</td>
</tr>
<tr>
<td>50.9 cm H2O</td>
<td>-2.4 cm H2O</td>
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<tr>
<td>51.7 cm H2O</td>
<td>-28.5 cm H2O</td>
</tr>
<tr>
<td>41.5 cm H2O</td>
<td>+6.4 cm H2O</td>
</tr>
</tbody>
</table>

**Incontinence-quality of life total score**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Mean change at week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.0</td>
<td>+26.9</td>
</tr>
<tr>
<td>35.1</td>
<td>+10.8</td>
</tr>
<tr>
<td>37.5</td>
<td>+24.4</td>
</tr>
<tr>
<td>35.7</td>
<td>+11.7</td>
</tr>
</tbody>
</table>

SD= standard deviation, IDC= involuntary detrusor contraction
P<0.05 for all comparisons of botulinum toxin type A 200 units versus placebo

In study 515, 58% (240/416) of patients received a second treatment and in study 516 the proportion was 50% (137/275). At week six, there were statistically significant decreases in weekly urinary incontinence episodes from study baseline and treatment cycle baseline for all groups in both studies.

A pooled analysis of the studies is available and includes a subgroup analysis of MS (n=381) and SCI (n=310) patients. At week six, botulinum toxin type A 200 units had significantly decreased weekly urinary incontinence episodes (-22.6 in MS subgroup and -19.6 in SCI subgroup) compared with placebo (-14.0 in MS subgroup and -6.4 in SCI subgroup). Significant results in favour of botulinum toxin type A 200 units were also shown for the anticholinergic user (n=379) and non-anticholinergic user (n=312) subgroups. In the total pooled population, the median time for patient request for re-treatment was significantly longer for botulinum toxin type A 200 units (269 days) than placebo (92 days).

Patients who completed studies 515 or 516 could enter a long-term (three-year) extension study, where an interim analysis is available for treatments one to five. Patients received botulinum toxin type A at the dose to which they had previously been randomised, but following a protocol amendment in 2011, all patients subsequently received botulinum toxin type A 200 units. The same administration schedule was used but the re-treatment criteria differed, and were as follows: patient initiated request; and ≥1 urinary incontinence episode (recorded in patient diary) within three days of a study visit; and ≥12 weeks since previous treatment. The primary efficacy measure was mean change from baseline in number of weekly urinary incontinence episodes, assessed at week six after each treatment.

An interim analysis has reported on 387 patients (botulinum toxin type A 200 units [n=202] and 300 units [n=185]). A total of 336 patients received two treatments, 241 received three treatments, 113 received four treatments and 46 received five treatments. In the subgroup of patients treated with botulinum toxin type A 200 units the mean change from baseline to
week six in weekly urinary incontinence episodes were -22.7, -23.3, -23.1, -25.3, and -31.9 for treatments one to five respectively and the proportions of 100% responders were 44%, 44%, 46%, 36% and 44%, respectively.

**Summary of evidence on comparative safety**

In study 515, overall, 84% of patients (113/135) in the botulinum toxin type A 200 unit group and 74% of patients (107/145) in the placebo group reported an adverse event. Serious adverse events were reported in 13% (17/135) and 9.7% (14/145) of patients, respectively during treatment cycle one. Seven patients discontinued from the study due to adverse events during treatment cycle one, including two patients in the botulinum toxin type A 200 unit group (due to hydronephrosis and eschar). In study 516, overall, 87% of patients (79/91) in the botulinum toxin type A 200 unit group and 74% of patients (67/90) in the placebo group reported an adverse event. Five patients discontinued from the study due to adverse events during treatment cycle one, including three patients in the botulinum toxin type A 200 unit group.

The most common adverse events reported in both studies were urinary tract infection (49% to 56% for botulinum toxin type A 200 units and 34% to 40% for placebo) and urinary retention (20% for botulinum toxin 200 type A units and around 3.4% for placebo). In the subgroup of patients not using clean intermittent catheterisation at baseline, the proportion of patients who catheterised for urinary retention any time during the treatment one cycle was higher in the botulinum toxin type A 200 units group (31% [27/86] for MS patients and 27% [6/22] for SCI patients) than placebo group (4.5% [4/88] for MS patients and 19% [3/16] for SCI patients).

In study 515, autonomic dysreflexia was reported in three patients in the botulinum toxin type A 200 unit group, three patients in the 300 unit group and one patient in the placebo group. This occurred between days one to five in six patients and was considered related to the injection procedure. In study 516, autonomic dysreflexia was reported in one patient each in the botulinum toxin type A groups.

After treatment, no patient was found to have neutralising antibodies against botulinum toxin type A in either study. There were a total of four deaths and none was considered to be related to study treatment.

**Summary of clinical effectiveness issues**

In two phase III, double-blind, placebo-controlled studies, in which all patients received BSC, botulinum toxin type A 200 units was significantly superior to placebo for mean reduction from baseline to week six in the weekly urinary incontinence episodes. Results of the secondary endpoints were supportive of the primary endpoint. Overall, the treatment effect of botulinum toxin type A was shown in the MS and SCI subgroups regardless of anticholinergic use and efficacy did not appear to diminish with age.

However, the studies have some limitations. Firstly, there are currently limited re-treatment data available and this is noted in the summary of product characteristics. While the phase III studies were not designed specifically to assess re-treatment, there are some data available from the interim analysis of an open-label extension study. Secondly, discontinuation rates were high (13% to 16%) although were generally similar between treatment groups. Thirdly, in study 515, 46 patients received re-treatment without meeting the re-treatment criteria and the UK public assessment report noted a high number of
There was a high placebo response rate; in the pooled analysis 39% of placebo-treated patients had ≥50% decrease in weekly urinary incontinence episodes from baseline and 9.1% had a 100% decrease. However, response rates for botulinum toxin type A 200 units were consistently significantly higher than for placebo.

There are limited treatment options beyond BSC for patients not adequately managed with anticholinergics, with clinical experts consulted by SMC reporting unmet need. Botox® is the first botulinum toxin type A preparation licensed for urinary incontinence. However, off-label use of botulinum toxin type A preparations for urinary incontinence has been reported by clinical experts. The introduction of botulinum toxin type A may have implications for the service and for patients, as administration requires general or local anaesthesia with or without sedation.

**Summary of comparative health economic evidence**

The company submitted a cost-utility analysis comparing botulinum toxin type A 200 units plus BSC to BSC only in an adult population with neurogenic detrusor overactivity (NDO) due to SCI (traumatic or non-traumatic) or MS, who are not adequately managed with anticholinergic medication. BSC was assumed to comprise behavioural therapy and incontinence pads (alone or in combination with clean intermittent catheterisation [CIC]), and anticholinergic medicines.

A Markov model was used, based on a five year time horizon and built from an NHS Scotland perspective. Health states in the model were based on a percentage reduction in urinary incontinence (UI) episodes from baseline: dry responders, non-dry responders (≥50-99% reduction in UI episodes) and non-responders (<50% reduction in UI episodes). Each model cycle was six weeks, while the mean time to botulinum toxin type A 200 units retreatment was estimated to be approximately nine months. Patients who did not respond to botulinum toxin type A 200 units were assumed to move to BSC. In both treatment arms, a small proportion of patients who did not respond were assumed to undergo bladder surgery.

Many of the data estimates used in the economic model were derived from the pooled results of the pivotal studies, with the proportions of patients moving to each health state based on an additional analysis of the primary endpoint of the pivotal studies. Response was based on the week 12 (cycle two) data, since this was the last point before a large proportion of the BSC patients in both studies crossed over to the botulinum toxin type A 200 units arm. Treatment effect was assumed to reduce over time until re-treatment, with each re-treatment assumed to be equally efficacious as the previous treatment.

Quality of life was measured in the pivotal studies using an adapted disease-specific Incontinence-Quality of Life questionnaire (I-QoL). Rather than map this questionnaire onto a generic measure, utility values for inclusion in the model were estimated via a sample of I-QoL health state vignettes in combination with the time trade-off technique. The utility
values for each health state in the model were as follows; dry responder 0.56, non-dry responder 0.44, and non-responder 0.24.

Resource use included the cost of botulinum toxin type A 200 units and the main costs associated with BSC: anticholinergic medication, incontinence pads and CIC. Other costs included the administration of botulinum toxin type A 200 units and BSC, outpatient urology appointments, treatment for urinary tract infection, and surgery.

The base case incremental cost per quality-adjusted life year (QALY) was £2,541, based on an incremental cost of £1,156 and QALY gain of 0.45. For patients with NDO due to MS, the cost per QALY was £5,514, based on an incremental cost of £2,343 and QALY gain of 0.43. For patients with NDO due to SCI, botulinum toxin type A 200 units was found to be dominant, based on a saving of £231 and a QALY gain of 0.35. This saving was largely the result of a relatively high resource use in the SCI BSC arm.

A number of one-way sensitivity analyses were provided. However, variations to the model point estimates were small (typically one standard error or ±10%) and only one of the analyses pushed the original cost per QALY outside a range of £2,000 to £3,000. The company also provided a number of scenario analyses, designed to test some of the model assumptions. Only an extremely conservative time horizon of 12 weeks substantially increased the cost per QALY (to £15,679).

There are a number of uncertainties associated with the analysis:

- The resource costs in the model underestimate the cost of hospital appointments. Applying the relevant total cost figures from the Information Services Division cost book, for both day case and outpatient appointments, increased the overall cost per QALY to £7,345.
- SMC had concerns about the face validity of the utility values produced from the company’s analysis but appreciated that it was the difference in utility values which drove the results. However, there is considerable uncertainty surrounding the utility differentials for these model health states. A range of 0.32 between the best and worst health states is an optimistic assumption based on similar published studies. Using a more conservative range of 0.12 between the best and worst health states increased the overall cost per QALY to £6,199.
- Additional analysis combining both the cost and utility uncertainties noted above resulted in an overall cost per QALY of £17,920; for the MS and SCI subgroups, the changes increased the cost per QALY to £28,454 and £11,415 respectively. However, it is acknowledged that this represents a conservative analysis.
- The company has taken an unusual approach to modelling patient transitions through the model. Patients are assumed to remain in their week-12 health state for the duration of the model. However, the company has factored in a time-dependent utility decrement to capture a reduction of efficacy between treatment cycles. These utility decrements have been calculated based on the proportion of patients that would move from one health state to another after each model cycle, yet the patients are not actually assumed to move in the model. Although this has enabled the company to capture a wearing off of treatment between treatment cycles, the fact that patients remain in their original health state means that any extra costs associated with this wearing off (e.g. increased incontinence pad use, visits to urologist) are not captured. Although the company was unable to provide further analysis to alleviate this concern, the impact of this uncertainty is not expected to be large enough to affect the overall conclusions.
- It is to be expected that the number of incontinence pad uses is higher in the BSC arm. However, as supported by SMC expert responses, it is less expected that the economic model assumes that the number of CIC uses is also higher in the BSC arm, especially
since botulinum toxin type A 200 units is expected to increase the need to catheterise (as implied as part of the licensed indication). For patients in the pivotal studies who do not use CIC at baseline, botulinum toxin type A 200 units leads to a statistically significant increase in CIC use at week six and week 12. However, the overall CIC difference for all patients in the pivotal studies was not statistically significant. Furthermore, a difference in CIC use between the two treatment arms is incorporated in the MS subgroup analysis, so this may be viewed as a worst case scenario in relation to this uncertainty.

- There is some minor concern surrounding the submitting company’s choice of comparator. SMC clinical experts indicated that off-label botulinum toxin type A preparations are already used in clinical practice, and also that sacral neuromodulation is a treatment option for this patient group. However, overall, the submitting company’s approach was deemed to be appropriate.

Despite the above uncertainties, the economic case has been demonstrated.

**Summary of patient and public involvement**

Patient Interest Group submissions were made by the:
- MS Society
- Bladder and Bowel Foundation

**Additional information: guidelines and protocols**

The National Institute for Health and Care Excellence (NICE) clinical guideline 148; urinary incontinence in neurological disease was published in 2012.6 The following advice is included for treatment to improve bladder storage.

- **Behavioural management programme** (e.g. timed voiding, bladder retraining and habit retraining) for people with neurogenic lower urinary tract dysfunction.
- **Antimuscarinic drugs** to people with
  - spinal cord disease (for example, spinal cord injury or multiple sclerosis) and
  - symptoms of an overactive bladder such as increased frequency, urgency and incontinence.
- **Botulinum toxin type A** as bladder wall injection to adults:
  - with spinal cord disease (for example, spinal cord injury or multiple sclerosis) and
  - with symptoms of an overactive bladder and
  - in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

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

Before offering bladder wall injection with botulinum toxin type 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.

NB: the guideline also includes statements regarding use in spinal cord disease and consideration of use in children/young people, which are not included in the current marketing authorisation for botulinum toxin.
- **Augmentation cystoplasty**

The European Association of Urology updated their guideline on neurogenic lower urinary tract dysfunction in 2011.\(^7\) Drug treatments include antimuscarinic drugs (oxybutynin, trospium chloride, tolterodine tartrate, propiverine, darifenacin and solifenacin). Under “minimal invasive treatment” catheterisation (intermittent self- or third-party catheterisation) is noted and considered gold standard for the management of neurogenic lower urinary tract dysfunction. The guideline also notes that botulinum toxin injections in the bladder causes a long-lasting but reversible chemical denervation that lasts for about nine months.

### Additional information: comparators

None

### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per treatment (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Botulinum toxin type A</strong></td>
<td>200 units, as 1mL (~6.7 units) injections across 30 sites in the detrusor muscle</td>
<td>276</td>
</tr>
</tbody>
</table>

Cost from eVadis on 13 June 2013.

### Additional information: budget impact

The company submitted two different case types for the management of urinary incontinence in adult patients: the first for urinary incontinence in adult patients with NDO due to MS and the second for urinary incontinence in adult patients with SCI that cannot be adequately managed with anticholinergic medication. For both of the above cases, three different scenarios were submitted, with the following budget impact based on the scenario believed to be most relevant to NHS Scotland.

#### For MS Patients

The submitting company estimated the population eligible for treatment to be 656 in year 1 and 673 in year 5 in the base case, with an estimated uptake rate of 12.50% in year 1 and 40% in year 5. The company has also estimated that there will be a discontinuation rate of 16.40% in all 5 years.

The gross impact on the medicines budget was estimated to be £30k in year 1 and £98k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £24k in year 1 and £80k in year 5.

#### For SCI Patients

The submitting company estimated the population eligible for treatment to be 1,368 in year 1 and 1,604 in year 5 in the base case, with an estimated uptake rate of 15% in year 1 and 50% in year 5. The company has also estimated that there will be a discontinuation rate of 16.40% in all 5 years.
The gross impact on the medicines budget was estimated to be £82k in year 1 and £321k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £65k in year 1 and £254k in year 5.

All figures relate only to the medicines budget impact and therefore do not include the costs of administration.

In both cases, budget impact may be overestimated in the presence of existing off-label use of botulinum toxin type A for urinary incontinence.
References

The undernoted references were supplied with the submission. The one shaded grey is additional to those supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 16 August 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.