HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

# TRANSPARENCY COMMITTEE

## Opinion
## 19 November 2014

## BOTOX 50 ALLERGAN UNITS, powder for solution for injection
**Box of 1 vial (CIP: 34009 370 831 4 0)**
## BOTOX 100 ALLERGAN UNITS, powder for solution for injection
**Box of 1 vial (CIP: 34009 562 088 8 3)**
## BOTOX 200 ALLERGAN UNITS, powder for solution for injection
**Box of 1 vial (CIP: 34009 370 832 0 1)**

Applicant: ALLERGAN FRANCE SAS

| | |
|---|---|
| INN | Botulinum toxin type A |
| ATC code (2013) | M03AX01 (muscle relaxants, peripherally acting agents) |
| Reason for the review | **Extension of indication** |
| List concerned | **Hospital use (French Public Health Code L.5123-2)** |
| Indication concerned | **"Treatment of idiopathic overactive bladder associated with symptoms including:**<br>**- 3 episodes of urinary incontinence with urgency over 3 days, and**<br>**- urinary frequency defined by a number of urinations of ≥ 8 a day,**<br>**not adequately managed with anticholinergics (after 3 months of treatment) or intolerant to anticholinergic treatment and not responding to properly conducted physiotherapy."** |

| | |
|---|---|
| **Actual benefit:** | **Substantial** |
| **Improvement in actual benefit** | **BOTOX provides a minor improvement in actual benefit (level IV) in the treatment of overactive bladder in patients in whom drug and non-drug treatments have failed (behavioural treatments and rehabilitation of the perineum and the sphincter).** |
| **Therapeutic use** | **Second-line treatment after the failure of drug treatment (with anticholinergics and with beta-3 adrenoceptor agonists), behavioural treatments and rehabilitation of the perineum and the sphincter.** |
| **Recommendations** | |

# 01 ADMINISTRATIVE AND REGULATORY INFORMATION

| | |
|---|---|
| Marketing Authorisation (national procedure) | Date of initial Marketing Authorisation:<br>- 22 August 2000 for the dosage 100 Allergan units<br>- 22 February 2006 for the dosages 50 and 200 Allergan units.<br>Date of the extension of indication that is the subject of this review: 6 May 2014. |
| Prescribing and dispensing conditions /special status | List I<br>Medicinal product reserved for hospital use.<br><br>The administration of BOTOX requires the use of a procedure in the Joint Classification of Medical Procedures (CCAM) (section 8.2.3.12: the injection of botulinum toxin into the muscular wall of the bladder by cystourethroscopy). HAS gave a favourable opinion on the inclusion of this procedure in CCAM on 22 October 2012 in the context of the treatment of neurogenic detrusor overactivity in adults. The administration of BOTOX in the extension of indication to idiopathic forms is a result of that procedure. |

| | | |
|---|---|---|
| ATC Classification | 2013 | |
| | M | Musculo-skeletal system |
| | M03 | Muscle relaxants |
| | M03A | Muscle relaxants, peripherally acting agents |
| | M03AX | Other muscle relaxants, peripherally acting agents |
| | M03AX01 | botulinum toxin |

# 02 BACKGROUND

Application for inclusion for hospital use for the dosages 50 units, 100 units and 200 units of the proprietary medicinal product BOTOX (botulinum toxin type A) in the extension of indication: Treatment of idiopathic overactive bladder associated with symptoms including:

- 3 episodes of urinary incontinence with urgency over 3 days, and
- urinary frequency defined by a number of urinations of ≥ 8 times a day, not adequately managed with anticholinergics (after 3 months of treatment) or intolerant to anticholinergic treatment and not responding to properly conducted physiotherapy.

BOTOX 50, 100 and 200 Allergan units is already approved for hospital use in all these indications. As a reminder, it has achieved, in the "treatment of neurogenic detrusor overactivity leading to urinary incontinence not controlled by anticholinergic treatment in patients with spinal cord injuries and patients with multiple sclerosis who are self-catheterising to empty their bladder", and in these other indications of the Marketing Authorisation, a substantial AB and an IAB III.

# 03 THERAPEUTIC INDICATIONS

**"Adults**

Bladder dysfunction:

**Treatment of idiopathic overactive bladder associated with symptoms including:**

- **3 episodes of urinary incontinence with urgency over 3 days, and**
- **urinary frequency defined as number of urinations of ≥ 8 times a day, not adequately managed with anticholinergics (after 3 months of treatment) or intolerant to anticholinergic treatment and not responding to properly conducted physiotherapy.**

Treatment of neurogenic detrusor overactivity leading to urinary incontinence which is not controlled by anticholinergic treatment in:
- patients with spinal-cord injuries,
- patients with multiple sclerosis who are self-catheterising to empty their bladder.

Adults and children over 12 years of age
- Ocular motility disorders: strabism, recent ocular motility paralysis, recent thyrotoxic myopathy.
- Blepharospasm.
- Hemifacial spasm.
- Spasmodic torticollis.
- Severe axillary hyperhidrosis that does not respond to topical treatments leading to substantial psychological and social issues.

Adults and children aged 2 years and older
- Symptomatic topical treatment of spasticity (muscle hyperactivity) of the upper and/or lower limbs."

## 04 DOSAGE

"**General recommendations**
The recommended doses of BOTOX are not interchangeable with those for other botulinum toxin preparations. They are expressed in Allergan units. In cases where there is a history of neurogenic disorders of the face and in persons more than 70 years of age, it is recommended that the dosage should be reduced for the first session of injections.

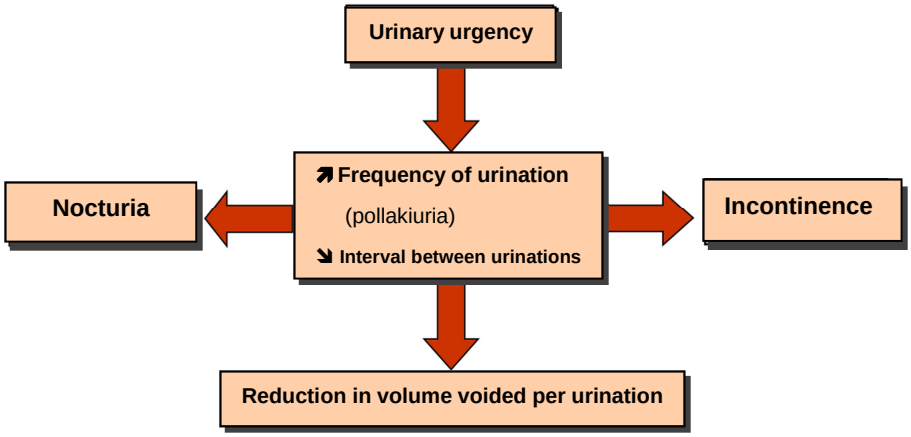
**Dosage and methods of administration in the treatment of overactive bladder**
Patients must be informed that clean intermittent catheterisation to empty their bladder may be required. They themselves or their caregivers must be able to carry it out.
Intravesical instillation of diluted anaesthetic solution can be administered with or without sedation before the injection, in accordance with local practice. If local anaesthetic instillation is performed, the bladder must be drained and rinsed with sterile saline before continuing with the injection procedure.
Start treatment with a dose of 50 units of BOTOX. If the response is not sufficient, the studied dose of 100 units of BOTOX could be used in the following injections.
The reconstituted BOTOX solution should be injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder must be instilled with enough saline to allow adequate visualisation of the injections, while avoiding excessive distension. The needle must be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 ml each should be spaced approximately 1 cm apart. The last injection must be given with 1 ml of sterile saline to ensure that the whole of the dose is injected. Once the injections have been given, the saline used to visualise the bladder walls must not be drained so that the patient can demonstrate his/her ability to urinate before leaving the healthcare organisation. The patient must remain under observation for at least 30 minutes after the injection and until spontaneous micturition is restored.
Clinical improvement is generally observed within the first 2 weeks after the injection. A new injection can be considered when the clinical benefit of the previous one is fading (mean duration of the effect observed in phase 3 studies with 100 units of BOTOX: 166 days (about 24 weeks)), leaving a minimum interval of 3 months between them."

**Injection technique**
Strictly intramuscular or strictly intradermal, according to the indication.
In adult patients with overactive bladder, this drug treatment given by injection into the detrusor must be included in an overall, multidisciplinary treatment involving a urologist and a gynaecologist-obstetrician who have received specific training in the use of botulinum toxin in this indication under the supervision of an urologist. Injections of botulinum toxin must be given under flexible or rigid cystoscopic guidance, avoiding the trigone.

## 05 THERAPEUTIC NEED

Overactive bladder is a clinical syndrome characterised by an irrepressible need to urinate (urgency) with or without incontinence, most often associated with increased urinary frequency and nocturia with no obvious urinary tract infection or local organic pathology likely to cause these symptoms. Among the symptoms of overactive bladder, urgency is the pivotal symptom as it constitutes the trigger for other potentially associated symptoms (Fig. 1).

***Fig. 1: Schematic diagram of overactive bladder syndrome (Chapple 2005)***




The risk factors for overactive bladder include age, one or more previous pregnancies, a history of vaginal birth and gynaeco-obstetric trauma, a history of pelvic or abdominal surgery, obesity, intensive physical activity and enuresis in childhood.

Several options are available for the treatment of idiopathic urinary incontinence caused by urge incontinence.[1,2] Behavioural treatments (adjustment of fluid intake, reprogramming of voiding, keeping a voiding calendar) and rehabilitation of the perineum and the sphincter are recommended (grade C). These different methods can be combined to achieve rehabilitation to inhibit bladder contractions. They can be proposed as first-line treatment, and may be an alternative to the drug treatment of urinary incontinence. An anticholinergic must be suggested as first-line treatment and/or after failure of behavioural treatment and/or rehabilitation (grade B). This drug treatment may be considered only if there is no urinary tract infection or urinary retention, and must not be combined with an anticholinesterase. Anticholinergics have proven efficacy by comparison with placebo, but this action is moderate in eliminating or relieving urinary urge incontinence, with a mean reduction of about one episode of urinary incontinence per period of 48 hours. Their main drawback lies in their safety profile: mainly dry mouth, constipation and cognitive disorders.

[1] National Health Accreditation and Assessment Agency. Management of urinary incontinence in women in general practure. Professional guidelines department May 2003; 136 p.
[2] Prof. François Haab (University of Paris VI, Tenon Hospital, Paris). Report on urinary incontinence sent to Mr Philippe Bas (Ministry of Health and Solidarity). April 2007.

According to the authors of a recent meta-analysis,[3] dry mouth is the effect most commonly observed (about 30% of patients on anticholinergics). Out of the proprietary medicinal products available in France, three (VESICARE, CERIS and TOVIAZ) have a safety profile better than that of DITROPAN, particularly in elderly patients. According to the latest guidelines from the European Association of Urology,[4] there are no clinical data proving that one anticholinergic is superior to another in terms of the improvement in symptoms of urinary incontinence, quality of life or behavioural therapy. According to the latest Canadian[5] and American guidelines,[6] all anticholinergics have similar efficacy and immediate-release oxybutynin generates more adverse effects than other anticholinergics.
Mirabegron (BETMIGA) is an alternative to anticholinergics. However, its short-term efficacy, which is modest by comparison with placebo, has not been compared with that of an anticholinergic. Its long-term safety profile is not known.
Minimally invasive and surgical techniques and palliative treatments (protectors, urine collection devices, urinary catheter, penile sheaths, etc.) can be considered in the event of inefficacy, contraindications or adverse effects linked to the medicines and in the most severe cases. Neuromodulation of the sacral roots is an alternative (minimally invasive technique), with urinary diversion and augmentation cystoplasty being considered as a last resort.

# 06 CLINICALLY RELEVANT COMPARATORS

## 06.1 Medicinal products

| Name (INN) *Company* | Same TC* Yes / No | Indication | Date of opinion | AB | IAB (wording) | Reimbursed Yes/No |
|---|---|---|---|---|---|---|
| **BETMIGA** (mirabegron) ASTELLAS PHARMA | No | Treatment of the symptoms of urinary urge incontinence and pollakiuria and/or urinary urge incontinence that may occur in adult patients with overactive bladder syndrome. | 5 February 2014 | Low | IAB V (non-existent) | Yes |

*Therapeutic category.

NB: The target population for BETMIGA is not quite identical to that of BOTOX. Anticholinergics are not an alternative: the prescription of BOTOX should be considered only in patients "not adequately managed with anticholinergics (after 3 months of treatment) or intolerant to anticholinergic treatment" according to the SPC.

## 06.2 Other health technologies

- Behavioural treatments: changing fluid intake, rescheduling micturition, keeping a micturition diary.
- Rehabilitation of the perineum and sphincter.

These different methods can be combined with drug treatments so as to achieve rehabilitation to inhibit bladder contractions.

- Surgical techniques:

[3] C. Roxburgh et al. Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. Cochrane Review 2009.
[4] M.G. Lucas et al. Guidelines on urinary incontinence. European Association of Urology 2014.
[5] Traitements visant la vessie hyperactive : accent sur la pharmacothérapie. Directive clinique de la société des obstétriciens et gynécologiques du Canada. J Obstet Gynaecol Can 2012 ;34 :S1-S12
[6] E.A. Gormley et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: American Urological Association Guideline. 2012.

- Neuromodulation of the sacral roots (using an implantable medical device).
- Bladder enlargement surgery.

### ◗ Conclusion

**The relevant comparators for BOTOX are: mirabegron (BETMIGA) as an alternative to anticholinergics, and less invasive surgical techniques (functional neuromodulation).**

# 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

BOTOX in the indication urinary incontinence due to overactive bladder is reimbursed in the vast majority of European countries and in the United States of America.

| Country | REIMBURSEMENT | |
|---|---|---|
| | YES/NO<br>If not, why not | Target populations<br>Marketing Authorisation or restricted population |
| USA | Yes | MA, injection at a day surgery centre or in the doctor's surgery |
| Germany | | MA, injection externally or during a stay in hospital |
| Norway | | MA, injection in healthcare establishment or in general practice |
| Sweden | | |
| Portugal | | MA, injection externally or during a stay in hospital |
| United Kingdom | | MA, injection externally or during a stay in hospital (NICE opinion) |
| Poland | | MA, injection in healthcare organisation |
| Italy | | |
| Spain | | |
| Greece | | |
| Netherlands | | |
| Austria | | |
| Malta | | |
| Denmark | | |
| Finland | | |
| Iceland | | |
| Russia | Yes | MA, reimbursement for veterans and disabled patients |
| Ireland | | |
| Belgium | | |
| Luxembourg | | |
| Switzerland | | |
| Croatia | No (dossiers not yet submitted) | |
| Czech Republic | | |
| Estonia | | |
| Hungary | | |
| Turkey | Under assessment | |

# 08 ANALYSIS OF AVAILABLE DATA

The company has submitted three controlled studies in the treatment of idiopathic overactive bladder:

- a phase II dose/response study (No. 191622-077) comparing the efficacy and safety of BOTOX (50 U, 100 U, 150 U, 200 U and 300 U) with those of placebo;
- two pivotal phase III studies (No. 191622-**095** and 191622-**520**) comparing the efficacy and safety of BOTOX (100 U) with those of placebo;
- a follow-up study (study 191622-096) in patients who completed the two pivotal phase III studies. This study is still in progress. Preliminary results (3rd interim analysis) are presented for information purposes.

## 08.1 Efficacy

### 8.1.1 Dose-finding study (191622-077)

**Objective of the study:**
The objective of this study was to evaluate the efficacy and safety of BOTOX at various dosages in patients with idiopathic overactive bladder with urinary incontinence for at least 6 months and who are inadequately managed by anticholinergic treatment.

**Methods:**
This was a multicentre, randomised, double-blind, parallel-group study versus placebo. Patients were randomised to one of the following treatment groups: BOTOX 50, 100, 150, 200, 300 units or placebo. Treatment was administered via cystoscopy as 20 intramuscular injections of 0.5 ml given into the detrusor, avoiding the trigone and the dome.

Patient inclusion criteria:

- adults with at least eight episodes of urinary incontinence a week, and urination at least eight times a day;
- insufficiently managed by one or more anticholinergic drugs;
- able to carry out clean intermittent self-catheterisation or agree to the insertion of an indwelling catheter.

Primary efficacy endpoint: mean reduction, compared with baseline, in the number of weekly episodes of urinary incontinence in the 12th week.

**Results:**
A total of 313 patients were randomised: 269 to the BOTOX groups and 44 to the placebo group.

Table 1: Populations analysed in the dose-finding study

| Treatment groups | BOTOX 300 U | BOTOX 200 U | BOTOX 150 U | **BOTOX 100 U** | **BOTOX 50 U** | Placebo |
|---|---|---|---|---|---|---|
| Randomised | 56 | 53 | 49 | **54** | **57** | 44 |
| ITT population | 56 | 53 | 49 | **54** | **57** | 44 |
| PP population | 47 | 47 | 43 | 48 | 49 | 34 |
| Safety population | 55 | 52 | 50 | **55** | **56** | 43 |

The demographic characteristics of the patients on inclusion did not differ between the treatment groups. The median age was 58.8 years (19-85 years), with a majority of women (92%). Only 11.5% (36/313) were aged 75 years or over.

Results for the primary efficacy endpoint (ITT analysis):

Table 2: Number of weekly episodes of urinary urge incontinence (UUI) in the placebo and BOTOX groups in the 12th week of the dose-finding study

| Treatment groups | Number of episodes of urinary urge incontinence a week | | |
|---|---|---|---|
| | **on inclusion** | **in the 12th week: difference in the number of UUIs between the BOTOX groups and the placebo group [95% CI]** | **p** |
| BOTOX 50 U | 26.8 (±20.84) | -5.8 [-11.27; -0.24] | 0.041 |
| BOTOX 100 U | 24.1 (±17.63) | -4.8 [-10.41; 0.83] | NS (0.09) |
| BOTOX 150 U | 28.3 (±26.28) | -8.9 [-14.60; -3.13] | 0.003 |
| BOTOX 200 U | 27.8 (±22.72) | -7.8 [-13.40; -2.14] | 0.007 |
| BOTOX 300 U | 30.3 (±18.98) | -6.7 [-12.32; -1.16] | <0.02 |
| Placebo | 32.5 (±20.24) | - | - |

NB: The results of a second dose-finding study[7] are not presented because patients with idiopathic overactive bladder but without urinary incontinence could be included (off label).

### 8.1.2 Phase III studies (191622-0958 and -520)

The objective and methods of these two studies were similar:

**Objective:**
To evaluate the efficacy and safety profile of botulinum toxin A (BOTOX 100 U) in the treatment of idiopathic overactive bladder with urinary incontinence in patients not adequately managed by anticholinergic treatment.

**Methods:**
Randomised, double-blind, parallel-group, multicentre studies versus placebo. Study 191622-095 was carried out in North America (64 centres in the United States and 8 centres in Canada). Study 191622-520 was carried out in Europe and the United States (64 centres in 7 countries). No patient was included in France.

Inclusion criteria:

- adults with symptoms of idiopathic overactive bladder for at least 6 months with at least three episodes of urinary urge incontinence on 3 consecutive days and urination at least eight times a day (and more than 24 urinations in the 3-day selection period);
- patients agreeing to use clean intermittent self-catheterisation (CISC) to empty their bladder;
- patients insufficiently controlled[9] by one or more anticholinergic drugs.

Study treatments:

- BOTOX 100 U and placebo. A second injection of BOTOX could be given to patients who meet all the following criteria: patient's request, presence of at least two episodes of urinary incontinence with urgency and no more than one day without an episode of urinary incontinence out of 3 days reported in the week before the second injection, post-void residual urine volume < 200 ml, a period of at least 12 weeks after the 1st injection.
- An antibiotic was prescribed one day before the start of the study treatment and continued for 3 days after the injection.
- Patients could not receive any anticholinergic treatment during the study.

[7] Denys P, et al. Efficacy and Safety of Low Doses of Botulinum Toxin Type A for the Treatment of Refractory Idiopathic Overactive Bladder: A multicentre, double-blind, randomised, placebo-controlled dose-ranging study. Eur. Urol. 2011, doi:10.1016/j.eururo.2011.10.028.
[8] Nitti V.W. et al. EMBARK Study Group. Onabotulinumtoxin A for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3 randomized placebo-controlled trial. J Urol 2013; 189: 2186-93.
[9] Patients incontinent after at least 4 weeks of an anticholinergic treatment at the optimum dose or in the event of adverse events occurring after at least 2 weeks of treatment.

Primary efficacy endpoints:

In the 12th week of treatment, the two primary efficacy endpoints were:

- the mean change in the number of episodes of urinary incontinence per 24 hours recorded by the patient in the 3 days before the visit, assessed using analysis of covariance;
- the proportion of patients with a positive response to treatment according to the TBS score,[10] assessed using a Cochran-Mantel-Haenszel test.

The secondary endpoints (evaluated in the 12th week) included:

- number of urinations per 24 hours;
- number of episodes of urinary (urge) incontinence per 24 hours;
- mean volume voided (ml);
- proportion of "responder" patients: proportion of patients with a reduction of at least 50% in the number of weekly episodes of urinary incontinence;
- proportion of "continent" patients: proportion of patients with a reduction of 100% in the number of weekly episodes of urinary incontinence;
- quality of life assessed using the I-QOL[11] and King's Health questionnaires[12] (scores for the items "role limitations" and "social limitation").

Method of analysing the results

The number of subjects needed was determined as follows:

- for the number of episodes of urinary incontinence per 24 hours: a total of 227 patients per group was needed to have a power of 82% and to detect a difference of 2.3 episodes of urinary incontinence over a period of 3 days. The calculation was based on a standard deviation of 8.5, a two-tailed test and a significance level of 5%.
- for the proportion of patients with a positive response at week 12: a total of 227 patients per group gave a power of 99% to detect a difference of 22% between the two groups (76% for the BOTOX group and 54% in the placebo group). The number of 227 was increased to 267 per group to take account of any patients who dropped out of the study early.

Randomisation was stratified by the number of episodes of urinary incontinence (≤ 9 versus > 9 reported over the 3-day selection period) and by centre. Subgroup analyses were done for age and sex.

The main analysis was carried out on the ITT population, managing missing data by the LOCF method.

The patients were followed up for at least 24 weeks and for up to 36 weeks in the case of second administration (second cycle of treatment).

[10] The TBS score (Treatment Benefit Scale) can be from 1 to 4 (1: greatly improved, 2: improved, 3: unchanged and 4: worse). Patients were considered to have a positive response to treatment according to the TBS score if their assessment with this score was 1 ("greatly improved") or 2 ("improved").

[11] The I-QOL score (Urinary Incontinence-Specific Quality of Life Instrument) goes from 0 (no quality of life) to 100 (optimal quality of life); it assesses three areas ("avoidance and limitation of behaviour", "psychosocial impact" and "social embarrassment".

[12] King's Health Questionnaire (KHQ): Self-assessment questionnaire that can be used to calculate a score for the impact of urinary incontinence on the general state of health, limitations on activity (role), physical or social limitation, relationships, emotions, sleep/energy and the severity of the symptoms of overactive bladder on the patient's everyday life. The score given for each of these sections is on a scale from 0 to 3 (0: not at all, 1: slightly, 2: moderately and 3: a lot).

**Results of the pivotal studies** (results in the ITT-LOCF population)

Characteristics of patients included

Table 3: Demographic characteristics of the patients on inclusion in pivotal studies 191622-095 and 191622-520

| Studies | 191622-095 | | 191622-520 | |
|---|---|---|---|---|
| Treatment groups | BOTOX n = 280 | Placebo n = 277 | BOTOX n = 277 | Placebo n = 271 |
| Age in years (SD*) | 61.7 years (12.7) | 61 years (13.1) | 59.5 years (12.7) | 59.2 years (14.1) |
| Sex (female) (%) | 252 (90.0%) | 245 (88.4%) | 244 (88.1%) | 229 (84.5%) |
| Duration of disease in years (SD) | 6.8 years (7.7) | 6.6 years (7.4) | 5.2 years (6.2) | 5.7 years (6.7) |
| Duration of anticholinergic treatment in weeks (SD) | 135.5 (166.6) | 118.2 (131.7) | 111.9 (139.7) | 111.5 (149.9) |
| Mean number of anticholinergic treatments (SD) | 2.4 (1.6) | 2.5 (1.6) | 2.3 (1.5) | 2.5 (1.5) |

*SD: standard deviation

Table 4: Characteristics of the patients' overactive bladder on inclusion in pivotal studies 191622-095 and 191622-520

| Studies | 191622-095 | | 191622-520 | |
|---|---|---|---|---|
| Treatment groups | BOTOX n = 280 | Placebo n = 277 | BOTOX n = 277 | Placebo n = 271 |
| Mean number of episodes of urinary incontinence per 24 hours (SD) | 5.5 (3.6) | 5.1 (3.2) | 5.5 (3.7) | 5.7 (3.9) |
| Mean number of episodes of urinary incontinence with urgency per 24 hours (SD) | 4.8 (3.2) | 4.5 (3.1) | 5.1 (3.6) | 5.2 (3.7) |
| Mean number of urinations per 24 hours (SD) | 12.0 (4.3) | 11.2 (3.1) | 12.0 (4.0) | 11.8 (3.6) |
| Mean number of episodes of urinary urge incontinence per 24 hours (SD) | 8.5 (4.7) | 7.9 (3.7) | 9.1 (4.6) | 8.8 (4.6) |
| Mean number of episodes of nocturia per 24 hours (SD) | 2.2 (1.5) | 2.0 (1.3) | 2.2 (1.5) | 2.1 (1.5) |
| Mean volume voided in ml (SD) | 156.4 (63.2) | 161.1 (68.7) | 144.2 (57.5) | 152.6 (59.3) |
| Mean post-void residual volume in ml (SD) | 27.7 (30.0) | 24.9 (27.0) | 17.2 (23.1) | 13.8 (20.7) |

The patients' characteristics were similar in the two groups in each of the two studies.

Results for the primary efficacy endpoints

In the 12th week, the number of episodes of urinary incontinence per 24 h was reduced from 1.65 or 1.91 by comparison with placebo in studies 095 and 520 respectively. The proportion of patients with a positive response in the TBS score for the BOTOX group was greater than that observed in the placebo group in the two studies (3.8 95% CI [2.7; 5.4] for study 095 and 4.6 95% CI [3.2; 6.6] for study 520, p < 0.001).

Table 5: Results for the primary efficacy endpoints of the two pivotal studies 191622-095 and 191622-520

| Studies | 191622-095 | | 191622-520 | |
|---|---|---|---|---|
| Treatment groups | **BOTOX** | **Placebo** | **BOTOX** | **Placebo** |
| **Number of episodes of urinary incontinence (UI)/24 h** | | | | |
| ITT-LOCF population, n | 280 | 277 | 277 | 271 |
| Value on inclusion (SD) | 5.47 (±3.62) | 5.09 (±3.20) | 5.52 (±3.75) | 5.70 (±3.86) |
| Value in the 12th week (SD) | 2.81 (±3.52) | 4.23 (±3.62) | 2.57 (±3.68) | 4.67 (±4.33) |
| Mean change (SD) | -2.65 (±3.33) | -0.87 (±2.83) | -2.95 (±3.58) | -1.03 (±3.00) |
| Difference vs placebo: adjusted mean* [95% CI]* | **-1.65 [-2.13; -1.17]** | | **-1.91 [-2.43; -1.39]** | |
| p* | **< 0.001** | | **< 0.001** | |
| **Proportion of patients with a positive response in the TBS score** | | | | |
| ITT-LOCF population, n | 278 | 271 | 274 | 269 |
| Proportion in the 12th week (%) | 169/278 (60.8%) | 79/271 (29.2%) | 172/274 (62.8%) | 72/269 (26.8%) |
| Odds ratio for BOTOX/placebo: adjusted mean** [95% CI]** | **3.8 [2.7; 5.4]** | | **4.6 [3.2; 6.6]** | |
| p** | **< 0.001** | | **< 0.001** | |

*****ANCOVA with adjustment for the variable

******Cochran-Mantel-Haenszel test

Results for the primary efficacy endpoints in patients who had a second administration of BOTOX

The median duration of the treatment effect in the two pivotal studies, based on a request to withdraw expressed by the patient, was 166 days (about 24 weeks).

Study 191622-095
353 patients (out of 557 in cycle 1) were eligible for a second treatment (cycle 2): 141 (50.3%) patients in the BOTOX group and 212 (76.5%) patients in the placebo group in cycle 1.

Study 191622-520
386 patients (out of 548 in cycle 1) were eligible for a second treatment (cycle 2): 163 patients (58.8%) in the BOTOX group, and 223 patients (82.3%) in the placebo group in cycle 1.

Table 6: Results for the primary efficacy endpoints after cycle 2 in studies 191622-095 and -520

| Studies | 191622-095 | | 191622-520 | |
|---|---|---|---|---|
| Treatment groups | **BOTOX/ BOTOX** | **Placebo/ BOTOX** | **BOTOX/ BOTOX** | **Placebo/ BOTOX** |
| **Number of episodes of urinary incontinence (UI)/24 h** | | | | |
| Value on inclusion **(cycle 1)** | | | | |
| N (number of patients) | 141 | 212 | 163 | 223 |
| Mean | **6.21** | **5.33** | **5.88** | **5.79** |
| Standard deviation | (±3.90) | (±3.19) | (±3.92) | (±3.77) |
| Value in the 12th week (cycle 2) | | | | |
| N | 135 | 199 | 152 | 208 |
| Mean | **3.10** | **2.20** | **2.42** | **2.05** |
| Standard deviation | (±3.05) | (±2.79) | (±3.24) | (±3.05) |
| Mean change | | | | |
| N | 135 | 199 | 152 | 208 |
| Mean | **-3.10** | **-3.18** | **-3.44** | **-3.71** |
| Standard deviation | (±3.71) | (±2.93) | (±3.45) | (±3.57) |
| Difference vs placebo: adjusted mean* [95% CI]* | **0.60 [-0.01; 1.20]** | | **0.43 [-0.16; 1.01]** | |
| p* | **NS (0.053)** | | **NS (0.153)** | |
| Value on inclusion **(cycle 2)** | | | | |
| N | 141 | 211 | 159 | 222 |
| Mean | **4.40** | **4.96** | **3.93** | **5.32** |
| Standard deviation | (±3.23) | (±3.52) | (±3.36) | (±4.11) |
| Value in the 12th week (cycle 2) | | | | |
| N | 135 | 199 | 152 | 208 |
| Mean | **3.10** | **2.20** | **2.42** | **2.05** |
| Standard deviation | (±3.05) | (±2.79) | (±3.24) | (±3.05) |
| Mean change | | | | |
| N | 135 | 199 | 152 | 208 |
| Mean | **-1.25** | **-2.78** | **-1.49** | **-3.23** |
| Standard deviation | (±2.47) | (±2.98) | (±2.58) | (±3.43) |
| Difference vs placebo: adjusted mean* [95% CI]* | **1.25 [0.72; 1.79]** | | **1.01 [0.47; 1.56]** | |
| p* | **< 0.001** | | **< 0.001** | |
| **Proportion of patients with a positive response in the TBS score (cycle 2)** | | | | |
| Value in the 12th week (cycle 2) | 97/133 (72.9%) | 158/202 (78.2%) | 112/150 (74.7%) | 167/211 (79.1%) |
| Odds ratio for BOTOX/placebo: adjusted mean** [95% CI]** | **0.75 [0.47; 1.25]** | | **0.78 [0.47; 1.27]** | |
| p** | **NS (0.268)** | | **NS (0.315)** | |

*****ANCOVA with adjustment for the variable
******Cochran-Mantel-Haenszel test

Results for the secondary endpoints:

Table 7: Results for secondary endpoints in study 191622-095

| Study | 191622-095 | |
|---|---|---|
| Treatment groups | **BOTOX** | **Placebo** |
| **Mean number of urinations per 24 hours** | | |
| N*** | 280 | 270 |
| Value on inclusion (SD) | 11.98 (±4.26) | 11.20 (±3.07) |
| N | 263 | 258 |
| Value in the 12th week (SD) | 9.68 (±3.93) | 10.34 (±2.95) |
| Difference vs placebo* (adjusted mean, 95% CI) | **-1.04 [-1.48; -0.59]** | |
| p* | **< 0.001** | |
| **Mean number of episodes of urinary urge incontinence per 24 hours** | | |
| N | 280 | 277 |
| Value on inclusion (SD) | 8.54 (±4.68) | 7.85 (±3.65) |
| N | 263 | 258 |
| Value in the 12th week (SD) | 5.50 (±4.83) | 6.76 (±4.04) |
| Difference vs placebo* (adjusted mean, 95% CI) | **-1.51 [-2.15; -0.87]** | |
| p* | **< 0.001** | |
| **Mean volume voided (ml)** | | |
| N | 280 | 277 |
| Value on inclusion (SD) | 156.4 (±63.21) | 161.1 (±68.65) |
| N | 261 | 257 |
| Value in the 12th week (SD) | 198.3 (±96.97) | 171.7 (±83.72) |
| Difference vs placebo* (adjusted mean, 95% CI) | **30.3 [17.1; 43.5]** | |
| p* | **< 0.001** | |
| **Proportion of responder patients** (reduction of ≥ 50% in weekly episodes of UI between inclusion and the 12th week of the study) | | |
| n (%) | 161/280 (57.7%) | 80/277 (28.9%) |
| p** | **< 0.001** | |
| **Proportion of continent patients** (reduction of 100% in weekly episodes of UI between inclusion and the 12th week of the study) | | |
| n (%) | 64/280 (22.9%) | 18/277 (6.5%) |
| p** | **< 0.001** | |
| **Mean total score on the I-QOL quality of life questionnaire** | | |
| N | 280 | 277 |
| Value on inclusion (SD) | 36.5 (±20.6) | 37.3 (±19.4) |
| N | 266 | 255 |
| Value in the 12th week (SD) | 58.8 (±27.1) | 43.9 (±23.6) |
| Difference vs placebo* (adjusted mean, 95% CI) | **+14.9 [11.1; 18.7]** | |
| p* | **< 0.001** | |
| **Mean score for the "role limitations" field of the King's Health Questionnaire** | | |
| N | 278 | 277 |
| Value on inclusion (SD) | 61.2 (±30.4) | 56.2 (±30.1) |
| N | 266 | 255 |
| Value in the 12th week (SD) | 36.9 (±33.0) | 54.4 (±32.1) |
| Difference vs placebo* (adjusted mean, 95% CI) | **-20.64 [-25.56; -15.73]** | |
| p* | **< 0.001** | |
| **Mean score for the "social limitation" field of the King's Health Questionnaire** | | |
| N | 278 | 276 |
| Value on inclusion (SD) | 40.5 (±30.7) | 39.4 (±30.1) |
| N | 266 | 255 |
| Value in the 12th week (SD) | 22.6 (±28.1) | 36.0 (±31.1) |
| Difference vs placebo* (adjusted mean, 95% CI) | **-13.89 [-18.07; -9.71]** | |
| p* | **< 0.001** | |

*****ANCOVA with adjustment for the variable
******Cochran-Mantel-Haenszel test
***ITT-LOCF population

Table 8: Results for secondary endpoints in study 191622-520

| Study | 191622-520 | |
|---|---|---|
| Treatment groups | **BOTOX** | **Placebo** |
| **Mean number of urinations per 24 hours** | | |
| N*** | 277 | 270 |
| Value on inclusion (SD) | 12.01 (±4.07) | 11.77 (±3.65) |
| N | 264 | 260 |
| Value in the 12th week (SD) | 9.47 (±4.09) | 10.92(±3.68) |
| Difference vs placebo* (adjusted mean, 95% CI*) | **-1.72 [-2.19; -1.26]** | |
| p* | **< 0.001** | |
| **Mean number of episodes of urinary urge incontinence per 24 hours** | | |
| N | 277 | 270 |
| Value on inclusion (SD) | 9.11 (±4.63) | 8.78 (±4.49) |
| N | 264 | 260 |
| Value in the 12th week (SD) | 5.40 (±5.17) | 7.49 (±4.9) |
| Difference vs placebo* (adjusted mean, 95% CI*) | **-2.44 [-3.09; -1.79]** | |
| p* | **< 0.001** | |
| **Mean volume voided (ml)** | | |
| N | 275 | 270 |
| Value on inclusion (SD) | 144.2 (±57.54) | 152.5 (±59.27) |
| N | 264 | 258 |
| Value in the 12th week (SD) | 188.6 (±86.48) | 166.5 (±72.48) |
| Difference vs placebo* (adjusted mean*, 95% CI*) | **30.4 [19.8; 41.0]** | |
| p* | **< 0.001** | |
| **Proportion of responder patients** (reduction of ≥ 50% in weekly episodes of UI between inclusion and the 12th week of the study) | | |
| n (%) | 176/277 (63.5%) | 90/271 (33.2%) |
| p** | **<0.001** | |
| **Proportion of continent patients** (reduction of 100% in weekly episodes of UI between inclusion and the 12th week of the study) | | |
| n (%) | 87/277 (31.4%) | 28/271 (10.3%) |
| p** | **< 0.001** | |
| **Mean total score on the I-QOL quality of life questionnaire** | | |
| N | 274 | 270 |
| Value on inclusion (SD) | 31.7 (±16.98) | 32.1 (±17.24) |
| N | 262 | 255 |
| Value in the 12th week (SD) | 54.9 (±27.74) | 38.8 (±22.03) |
| Difference vs placebo* (adjusted mean*, 95% CI*) | **+16.9 [13.2; 20.6]** | |
| p* | **< 0.001** | |
| **Mean score for the "role limitations" field of the King's Health Questionnaire** | | |
| N | 275 | 270 |
| Value on inclusion (SD) | 69.6 (±26.83) | 66.4 (±26.84) |
| N | 263 | 257 |
| Value in the 12th week (SD) | 43.3 (±33.32) | 61.5 (±30.28) |
| Difference vs placebo* (adjusted mean*, 95% CI*) | **-19.8 [-24.8; -14.7]** | |
| p* | **< 0.001** | |
| **Mean score for the "social limitation" field of the King's Health Questionnaire** | | |
| N | 275 | 270 |
| Value on inclusion (SD) | 49.1 (±31.46) | 45.4 (±30.80) |
| N | 263 | 257 |
| Value in the 12th week (SD) | 32.9 (±32.48) | 43.6 (±31.96) |
| Difference vs placebo (adjusted mean*, 95% CI*) | **-13.2 [-17.8; -8.6]** | |
| p* | **< 0.001** | |

*****ANCOVA with adjustment for the variable
******Cochran-Mantel-Haenszel test
*** Number of patients in the ITT-LOCF population

Analysis of the results for the secondary endpoints at week 12 suggests an effect in favour of BOTOX 100 U by comparison with placebo in terms a reduction in the number of urinations per 24 hours, the number of episodes of urinary urge incontinence (urge incontinence) per 24 hours

and the mean volume voided. Similarly, the proportion of "responder" patients (with a reduction of ≥ 50% in weekly episodes of UI) and the proportion of "continent" patients (with a reduction of 100% in weekly episodes of UI) was larger in the BOTOX 100 U group than with placebo.
An improvement in quality of life was also observed with BOTOX in the score on the I-QOL quality of life questionnaire and in the "role limitations" and "social limitation" items of the King's Health Questionnaire (KHQ).

Results of the subgroup analyses

- According to sex

In the two pivotal studies, women were in the majority (970 women out of 1105 patients included, i.e. 87.8% women). The subgroup analyses showed that the treatment effect was not uniform according to sex, in the primary efficacy endpoints, with a reduction in the number of episodes of urinary incontinence in the 12th week with BOTOX that was larger in women than in men, considering that no difference between the BOTOX group and the placebo group was shown in the subgroup of men. Similarly, the proportion of patients with a positive response in the TBS score was smaller in men than in women.
These data must however be interpreted with caution, and a lack of power might explain them.

- According to age

The analyses compared four age groups: < 40 years, 40-64 years, 65-74 years and ≥ 75 years. These analyses showed a similar treatment effect with BOTOX (non-significant difference) between these age groups in terms of the reduction in the number of episodes of urinary incontinence in the 12th week and the response in the TBS score. Similar results were observed for the comparison of results between the patients < 65 years and the patients ≥ 65 years.

- According to the initial number of episodes of urinary incontinence (≤ 9 and > 9)

No significant difference in the treatment effect in the 12th week was shown between the two subgroups.

### 8.1.3 Follow-up study (191622-096)

**Methods:**
During this non-comparative study, patients who had completed the phase III pivotal studies (191622-095 and -520) and had been followed up for 24 weeks after the first injection and for at least 12 additional weeks in the event of a second injection received a new administration of BOTOX (cycle 1 of the study) within 21 days after the last administration. Several cycles of the administration of BOTOX were possible. The assessment was made 12 weeks after each cycle using the same criteria as in the pivotal studies, given that provision was made for a maximum of 12 cycles, corresponding to 3 years' follow-up. Patients could receive 100 or 150 units of BOTOX.

**Results:**
Out of the 967 patients (1105 randomised patients) who completed the pivotal studies, 839 were included in this follow-up. Results are available for 829 of them, 543 of whom received BOTOX 100 U and 286 patients BOTOX 150 U (off-label dosage). The results of an interim analysis (study still in progress) for patients who received up to 5 cycles of treatments are presented in the table below.

Table 9: Results for the primary* and secondary** efficacy endpoints in the 12th week for each cycle in study 191622-096

| Parameters | Cycle 1 n=829 | Cycle 2 n=603 | Cycle 3 n=351 | Cycle 4 n=216 | Cycle 5 n=137 |
|---|---|---|---|---|---|
| Mean number of episodes of urinary incontinence per 24 h* | -3.26 [-3.5; -3.02] | -3.70 [-3.97; -3.42] | -3.87 [-4.25; -3.49] | -3.20 [-3.76; -2.63] | - 3.22 [-3.99; -2.46] |
| Proportion of patients with a positive response in the TBS* score | 74% | 80.9% | 80.4% | 79.4% | 86.1% |
| Mean number of urinations per 24 h** | -2.56 [-2.76; -2.36] | -2.91 [-3.16; -2.66] | -2.81 [-3.16; -2.46] | -2.37 [-2.88; -1.86] | -2.55 [-3.24; -1.86] |
| Mean number of episodes of urinary urge incontinence per 24 hours | -3.81 [-4.09; -3.54] | -4.08 [-4.41; -3.75] | -4.19 [-4.65; -3.73] | -3.66 [-4.29; -3.04] | -3.77 [-4.66; -2.88] |
| Mean volume voided (ml)** | 51 ml [45.6; 56.3] | 55.9 ml [50; 61.8] | 54.2 ml [45.3; 63.1] | 48.4 ml [37.3; 59.6] | 48 ml [34; 62] |
| Mean I-QOL score** | +26 [24.3; 27.7] | +28.5 [26.5; 30.5] | +26.6 [24.1; 29] | +25.4 [21.8; 29] | +26.6 [22.2; 31] |
| Mean KHQ (role limitations)** | -28.5 [-30.9; -26.2] | -31.8 [-34.6; -29] | -28.7 [-32.4; -25] | -29.8 [-34.5; -25.1] | -30.6 [-37.4; -23.7] |
| Mean number of episodes of nocturia per 24 h** | -0.57 [-0.66; -0.49] | -0.61 [-0.7; -0.51] | -0.69 [-0.82; -0.55] | -0.56 [-0.74; -0.38] | -0.62 [-0.88; -0.35] |
| Mean KHQ (role limitations)** | -18.4 [-20.4; -16.4] | -19.8 [-22.2; -17.4] | -17.2 [-20.4; -14] | -18.3 [-22.7; -14] | -21.3 [-26.9; -15.7] |

These results, although suggesting the maintenance of efficacy on the readministration of BOTOX, must be interpreted with caution, since three hundred and fifteen (315) patients (38% of the population) ended the follow-up prematurely. Moreover, these are interim results, since the study is still in progress for 504 patients (60.8% of the population), with the populations greatly reduced after two cycles of treatment, and no control group.

## 08.2 Adverse effects

### 8.2.1 Data from clinical studies

These data are from dose-finding study 077 and the two pivotal studies (095 and 520), i.e. 1205 patients, 607 of whom received BOTOX 100 U. The median duration of exposure to BOTOX 100 U was about 24 weeks [min 1 week to max 45.6 weeks]. Only 291 patients in the BOTOX 100 U group were exposed for more than 24 weeks and 110 for more than 30 weeks.
Follow-up was carried out for up to 24 weeks for patients who had received a single administration (i.e. 291 patients in the BOTOX 100 U group for the 1st cycle of treatment) and up to 36 weeks for the 594 patients who received a second administration of BOTOX.

There were very few drop-outs on account of adverse effects after the 1st cycle of treatment: 1.5% (9/607) in the BOTOX 100 U group and 1% (6/585) in the placebo group.

At least one adverse event was reported in 68.4% of patients in the BOTOX 100 U group and in 53.7% of patients in the placebo group during the 1st cycle of treatment. In the two pivotal studies, 22.3% (123/552) of patients in the BOTOX 100 U group and 15.9% (86/542) of patients in the placebo group had an adverse event linked to the injection procedure with, in particular, one urinary infection in 35 patients (6.3%) in the BOTOX 100 U group and in 10 patients (1.8%) in the placebo group, p <0.001.

Adverse effects affected more patients in the BOTOX 100 U group (29.2% of patients) than in the placebo group (17.3% of patients). The occurrence of a urinary infection, urinary retention or the presence of an abnormal volume of residual urine were more common in the BOTOX group than with placebo. There were no reported serious adverse effects or deaths.

Table 10: Adverse effects in ≥ 3% of patients during cycles 1 and 2 of treatment in the clinical studies

| Wording of the AE | Cycle 1 | | | Cycle 2 | |
|---|---|---|---|---|---|
| | BOTOX 100 n=607 | BOTOX 150 n=50 | Placebo n=585 | BOTOX 100 n=500 | BOTOX 150 n=94 |
| Total | 177 (29.2%)* | 20 (40%)* | 101 (17.3%) | 111 (22.2%) | 17 (18.1%) |
| Urinary tract infection | 49 (8.1%)* | 6 (12%)* | 13 (2.2%) | 35 (7%) | 6 (6.4%) |
| Urinary retention | 43 (7.1%)* | 13 (26%)* | 2 (0.3%) | 20 (4%) | 0 (0%) |
| Dysuria | 36 (5.9%) | 2 (4%) | 29 (5%) | 25 (5%) | 3 (3.2%) |
| Volume of residual urine | 20 (3.3%)* | 0 (0%) | 2 (0.3%) | 13 (2.6%) | 0 (0%) |

* statistically significant difference between the BOTOX and placebo groups (p < 0.001)

Urinary tract infections
Two urinary tract infections (1 pyelonephritis during the 1st cycle of treatment and 1 urosepsis) were regarded as severe in the BOTOX group.
Out of the 1242 patients included in the placebo-controlled clinical studies, 41.4% (n=514) were aged 65 years and over and 14.7% (n=182) 75 years and over. There was no difference in terms of safety profile between patients under 65 years of age and those aged 65 years and over, except for the greater incidence of urinary tract infections in the BOTOX (or placebo) groups in patients aged 65 years and over in comparison with younger patients.
Fifty per cent (50%) of patients in the BOTOX 100 U group who carried out self-catheterisation reported urinary tract infections during the 1st cycle of treatment (this percentage was 30% in patients receiving a second cycle of treatment).

Increase in post-void residual urine volume (PVRU) and urinary retention
Urinary retention is a side effect associated with the action mechanism of botulinum toxin. On inclusion, 99.8% of patients in both groups had a PVRU of ≤ 100 ml. Patients whose PVRU was

greater than 200 ml had to carry out clean intermittent self-catheterisation (CISC) in the event of a urinary tract infection.

Table 11: Initiation of effective clean intermittent self-catheterisation (CISC+) according to the level of post-void residual urine (PVRU) in clinical studies after one administration (cycle 1)

| | BOTOX 100<br>n = 552 | Placebo<br>n = 542 |
|---|---|---|
| **Post-void residual urine (PVRU)** | | |
| ≤ 100 ml (normal PVRU) | 60.1% (332/552)<br>of which ASIP+ = 0.2% (1/552) | 88% (477/542)<br>of which CISC+ = 0.2% (1/542) |
| > 100 and < 200 ml | 29.2% (161/552)<br>of which CISC+ = 0.4% (2/552) | 11.1% (60/542)<br>of which CISC+ = 0% (0/542) |
| > 200 and < 350 ml | 6.9% (38/552)<br>of which CISC+ = 2.3% (13/552)<br>and UI = 2.3% (13/552) | 0.1% (4/542)<br>of which CISC+ = 0% (0/542)<br>and UI = 0.2% (1/542) |
| ≥ 350 ml | 3.8% (21/552)<br>of which CISC+ = 3.6% (20/552)<br>and UI = 2.3% (13/552) | 0.2% (1/542)<br>of which CISC+ = 0.2% (1/542)<br>and UI = 0% (0/542) |

CISC+ = effective clean intermittent self-catheterisation
PVRU = post-void residual urine

The common adverse effects associated with the procedure are dysuria and haematuria. Self-catheterisation (CISC) had to be done in 6.5% of patients in the BOTOX 100 U group and in 0.4% of patients in the placebo group in the controlled clinical studies. The median duration of self-catheterisation in the 1st treatment cycle was 63 days [1-214 days] in the BOTOX 100 U group and 10.5 days [3-18 days] in the placebo group. The data on the repeated administration of BOTOX that are currently available report the same types of adverse effects.

Effects away from the injection site
No case has been reported in the literature.

Antitoxin antibody, seroconversion
No case has been reported in the literature.

### 8.2.2 PSUR data

For the period from 1 January 1990 to 31 December 2013, 628 pharmacovigilance cases (1152 adverse effects), of which 592 medically confirmed, were reported in the following indications: vesico-sphincter dyssynergia, bladder disorder, overactive bladder, neurogenic bladder, incontinence, urinary incontinence, micturition disorders, urinary urgency and pollakiuria. Out of these 628 cases, 163 (of which 154 medically confirmed, 260 adverse effects) were regarded as serious. The most commonly reported adverse effects were: urinary tract infection (107 cases), urinary retention (63), dry mouth (39), muscle weakness (38), dry eyes (30), constipation (29), asthaenia (26) and fatigue (18).

### 8.2.3 SPC data

According to the SPC, urinary tract infections and dysuria are "very common" in patients treated for overactive bladder with BOTOX. Urinary retention, an increase in post-void volume and pollakiuria are "common" adverse effects.

Irrespective of the indication, adverse effects (excessive muscle weakness, dysphagia, inhalation pneumopathy, which can be fatal) linked to the spread of the botulinum toxin away from the injection site have very rarely been reported.

Rare general allergic reactions (rash, erythema, pruritus, anaphylactic reaction) and pain/smarting at the injection site may also occur.

## 08.3 Usage data

In Europe, 134,562 vials of BOTOX 50 Allergan units, 1,654,337 vials of BOTOX 100 Allergan units and 72,431 vials of BOTOX 200 Allergan units were sold between 1 January 2012 and 31 December 2013, according to data supplied by the company. In urological indications, including the treatment of idiopathic overactive bladder, exposure to BOTOX is estimated to be[13] 1,215,754 patient-years.

## 08.4 Summary and discussion

In the treatment of idiopathic overactive bladder with urinary incontinence, the dosage used in the pivotal studies for botulinum toxin type A (BOTOX) is 100 U per cycle of administration. The choice of this dosage is not soundly based on the dose-finding study. In addition, in the pivotal phase III studies, treatment was started with a dosage of 100 U, with a possible increase to 150 U in the follow-up study. However, the SPC recommends starting treatment with 50 U and makes no provision for a dose increase. According to the assessment made by NICE, the recommended dosage varies from 100 U to reduce the risk of episodes of urinary retention, to 200 U for optimal efficacy. The choice of dosage is thus not soundly based.

Two phase III randomised, double-blind, multicentre, placebo-controlled clinical studies were carried out in patients with overactive bladder, with symptoms including urinary incontinence, urinary urge incontinence and pollakiuria. A total of 1105 patients whose symptoms were not adequately managed by anticholinergic treatment (insufficient response or intolerance) were randomised to receive either 100 units of BOTOX or placebo.
These studies included patients who had had at least 3 episodes of urinary incontinence caused by urinary urge on 3 consecutive days (a mean of between 5 and 5.7 episodes on inclusion) and urination at least eight times a day (mean between 11 and 12 on inclusion).
**In study 191622-095,** 557 patients were randomised, 280 patients to the BOTOX 100 U group and 277 patients to the placebo group. During the first cycle of treatment, 65 patients (11.7%) dropped out of the study early, 11.1% (31) in the BOTOX group and 12.3% (34) in the placebo group. The patients included had a mean age of 61 years and 89% were women.
**In study 191622-520,** 548 patients were randomised, 277 patients to the BOTOX 100 U group and 271 patients to the placebo group. The patients included had a mean age of 59 years and 86% were women. During the first cycle of treatment, 44 patients (8.0%) dropped out of the study early, 7.2% (20) in the BOTOX group and 8.9% (24) in the placebo group.
In the 12th week, the number of episodes of urinary incontinence per 24 h was reduced from 1.65 or 1.91 by comparison with placebo in studies 095 and 520 respectively. The proportion of patients with a positive response in the TBS score for the BOTOX group was greater than that observed in the placebo group in the two studies (3.8 95% CI [2.7; 5.4] for study 095 and 4.6 95% CI [3.2; 6.6] for study 520, $p < 0.001$). This demonstrates the superiority of BOTOX over placebo as regards these criteria.

At the end of the 12 weeks' follow-up and by comparison with placebo, an improvement in favour of BOTOX was also observed in the following secondary endpoints: daily frequency of urination (pollakiuria), number of episodes of urinary urgency, and nocturia. The volume voided was also

[13] BOTOX has been indicated in Europe since August 2011 in the treatment of urinary incontinence linked to neurogenic overactive bladder and, since December 2012 in the treatment of urinary incontinence linked to idiopathic overactive bladder.

significantly larger. The BOTOX treatment was associated with improvements in quality of life measured using the Incontinence Quality of Life (I-QOL) questionnaire (including avoidance and limiting behaviour, psychosocial impact, social embarrassment) and the King's Health Questionnaire (KHQ) including the impact of the incontinence, lack of self-confidence, social limitation, relationships, emotions, sleep/energy and ability to adapt).

The median duration of the treatment effect in the two pivotal studies, based on a request to withdraw expressed by the patient, was 166 days (about 24 weeks). These results did not differ according to the number of episodes of urinary incontinence on inclusion or according to age. On the other hand, the results do seem to differ according to sex, but the small number of men included makes any conclusion risky.

The main expected adverse effects are urinary tract infections and urinary retention necessitating self-catheterisation.

**Main discussion points regarding the data:**

1) The methods of the phase III studies do not throw up any particular methodological problems. The efficacy of BOTOX after one injection was correctly established by comparison with placebo after 12 weeks of treatment.

2) Transferability:
- Clinical data in men are very limited (12.22% of men in the phase III studies).
- BOTOX has not been evaluated in comparison with mirabegron (BETMIGA). Its role in relation to functional neuromodulation has still to be determined.

3) Expected data:
- Since the duration of the therapeutic effect of botulinum toxin type A is unpredictable and the number of reinjections needed to obtain an optimal therapeutic response has not been established, longer-term clinical data are needed. Similarly, the long-term safety profile (including the risk of urinary retention and/or urinary tract infections) has still to be assessed, particularly by comparison with other possible treatments (functional neuromodulation).

# 09 THERAPEUTIC USE

In the treatment of refractory idiopathic overactive bladder, with urinary incontinence and in cases where at least 3 months' treatment with an anticholinergic has failed, mirabegron (BETMIGA) may be an alternative. Functional electrostimulation, surgery (including neuromodulation of the sacral roots in the event of resistance to drug treatments), palliative treatments (protectors, urine collection devices, urinary catheter, penile sheaths, etc.) can also be considered as alternatives to drug treatments for urinary incontinence in the event of inefficacy, contraindications or adverse effects, and in severe cases. Enterocystoplasty for enlargement of the bladder is a third-line treatment.

Role of botulinum toxin type A

The efficacy of botulinum toxin type A (BOTOX) was established versus placebo in patients no longer receiving anticholinergics. It has not been evaluated in comparison with mirabegron (BETMIGA) or with functional neuromodulation. According to the available data, botulinum toxin type A (BOTOX) is a 2nd-line treatment which should be considered in cases where drug treatment with an anticholinergic and/or mirabegron has failed, and is an alternative to minimally invasive surgical techniques (implantation of a neuromodulation device[14]).

In 2011[15] the European Association of Urology advocated the use of botulinum toxin type A in patients with urinary urge incontinence that is refractory to anticholinergic treatment. A single injection of botulinum toxin type A is considered more effective than placebo in curing or treating urinary urge incontinence and in improving quality of life up to 12 months (level of evidence 1A). More recently, the British assessment institute (NICE) has advocated,[16] in women with idiopathic overactive bladder and urinary incontinence, the use of botulinum toxin type A only in patients who are refractory to conservative approaches, including 1st-line anticholinergic treatment. The recommended dose is 200 units for an optimum expected effect or 100 units if the patient wishes to limit the risk of having to use self-catheterisation. It is recommended that patients should be informed of the expected benefits (partial or even complete improvement in symptoms of overactive bladder), the occasional need to be able to carry out self-catheterisation, the increased risk of urinary tract infections, the uncertainties about the duration of the treatment effect, the number of injections needed and the long-term safety profile.

Methods of using BOTOX

According to French experts:[17]

- the injection should be given in the operating theatre or the endoscopy suite; it can be used after local anaesthesia of the urethra and bladder, possibly supplemented by the inhalation of nitrous oxide and sometimes under general anaesthesia;
- the bladder must not be overfilled (risk of perforation). Treatment must be given with 0.5 to 1 ml at 10 to 20 injection sites evenly distributed in the bladder, avoiding the ureteral meatus;
- leaving a bladder probe in situ is not recommended, except in the event of substantial haematuria. The patient must be monitored until micturition is resumed;

[14] Neuromodulation of the sacral roots consists in activating or inhibiting neuronal reflexes by electrically stimulating the sacral nerve roots that innervate the bladder, sphincter and perineum by means of an implantable neuromodulator.

[15] Guidelines on Urinary Incontinence. European Association of Urology European Urology 2011; 59: 387-400.

[16] Urinary incontinence. The management of urinary incontinence in women. Issued: September 2013 NICE clinical guideline 171. guidance.nice.org.uk/cg171

[17] Hermieu JF et al. Recommandations pour l'utilisation de la toxine botulinique de type A (BOTOX) dans l'hyperactivité vésicale réfractaire idiopathique. Progrès en urologie 2013;23:1457—1463.

- an information sheet about possible adverse effects must be given to the patient when he/she leaves. A consultation must be scheduled 3 months after the first injection (micturition calendar, flowmetry, post-void residual volume and cytobacteriological examination of the urine);
- a post-void residual volume that is > 200 ml and/or symptomatic must lead to a discussion of self-catheterisation;
- a new injection can be considered when the clinical benefit of the previous one is fading (between 6 and 9 months).

The SPC states that BOTOX must not be administered to patients with a urinary tract infection, with acute or chronic urinary retention when intermittent catheterisation is contraindicated or is rejected by the patient. Its use in pregnant women is not recommended.

# 010 TRANSPARENCY COMMITTEE CONCLUSIONS

**In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:**

## 010.1 Actual Benefit

◗ Idiopathic overactive bladder with urinary urge incontinence leads to a marked deterioration in the quality of life[18,19,20] (psychological implications for everyday activities and working life, particularly sleep disorders) and possible progression of social disadvantage.
◗ The efficacy/adverse effects ratio for botulinum toxin type A in this indication is high after one injection; it has still to be established in the event of long-term, multiple injections.

◗ Public health benefit

In terms of public health, urinary incontinence may give rise to a marked impairment of the quality of life and a source of disability in patients' everyday life, with major family and social consequences. The influence on public health of urinary incontinence in adult patients with idiopathic detrusor overactivity who are intolerant of anticholinergics or in whom they have failed can be rated as low. The symptomatic management of urinary incontinence in these patients is not a public health need.

The data from short-term clinical studies, i.e. those lasting 12 weeks, carried out with the proprietary medicinal product BOTOX versus placebo show a mean reduction of 1.65 to 1.91 daily episodes of urinary incontinence according to the studies and an improvement in quality of life on the I-QOL of 15.9 points, that was considered to be clinically relevant. In view of these facts, it is expected that the proprietary medicinal product BOTOX will have a moderate impact on patients' morbidity and quality of life. However, the transferability of these results is not yet assured in the long term because there are not enough data on the maintenance of the treatment's efficacy.

Moreover, a positive impact on the organisation of healthcare could be expected if treatment with BOTOX made it possible to delay recourse to more invasive treatments such as

[18] Coyne KS et al. The Impact of Urinary Urgency and Frequency on Health-Related Quality of Life in Overactive Bladder: Results from a National Community Survey. Value Health 2004; 7: 455-63.
[19] Irwin DE1, Milsom I, Kopp Z, Abrams P, Cardozo L. Impact of overactive bladder symptoms on employment, social interactions and emotional well-being in six European countries. BJU Int 2006; 97: 96-100.
[20] Papanicolaou S, Hunskaar S, Lose G, Sykes D. Assessment of bothersomeness and impact on quality of life of urinary incontinence in women in France, Germany, Spain and the UK. BJU Int 2005; 96: 831-8.

neuromodulation and possibly surgery. However, to date there are no data to show that this is the case.

Consequently, in the current state of knowledge, the expected impact of the proprietary medicinal product BOTOX on public health is low.

- BOTOX is intended as symptomatic therapy.
- It is a second-line therapy which should be considered after the failure of drug treatment (with anticholinergics and with beta-3 adrenoceptor agonists).
- There is a treatment alternative (mirabegron: BETMIGA). Surgical techniques with varying degrees of invasiveness can also be considered, among them functional neuromodulation and surgery to enlarge the bladder as a last resort.

**Taking account of these points, the Committee considers that the actual benefit of BOTOX is substantial in this extension of indication.**

**The Committee recommends inclusion on the list of medicines approved for hospital use in the indication "treatment of idiopathic overactive bladder with symptoms including 3 episodes of urinary urge incontinence over 3 days, and urinary frequency defined by a number of urinations of ≥ 8 a day, not adequately managed with anticholinergics (after 3 months of treatment) or intolerant to anticholinergic treatment and not responding to properly conducted physiotherapy" and at the dosages in the Marketing Authorisation.**

## 010.2 Improvement in actual benefit (IAB)

**BOTOX provides a minor improvement in actual benefit (level IV) in the treatment of overactive bladder in patients in whom drug and non-drug treatments have failed (behavioural treatments and rehabilitation of the perineum and the sphincter).**

## 010.3 Target population

The target population of BOTOX is made up of patients with idiopathic overactive bladder who have at least three episodes of urinary urge incontinence over 3 days, and urinate more than eight times a day. These patients have also failed treatment with anticholinergics (inefficacy after 3 months of treatment or intolerance) and with beta-3 adrenoceptor agonists and do not respond to properly conducted physiotherapy.

**Estimate/conclusion**

According to a European study[21] (Germany, Spain, France, Italy, United Kingdom, Sweden), the mean prevalence of overactive bladder is 16.6% in the population over 40 years of age. In France, prevalence in this population is 12%,[22] i.e. about 3.9 million people affected. The proportion of patients consulting doctors for this reason is 60%, i.e. about 2.4 million patients. Of these, at the time of the European transverse survey, only 27% were on drug treatment, and 36% had urinary incontinence. Applying these results to the French population, the population likely to be treated with medication for overactive bladder with urinary incontinence is around 233,000 patients. Assuming that the proportion of patients in whom anticholinergics failed is 50%, 117,000 patients would potentially be affected. The proportion of patients who also had failure of beta-3 adrenoceptor agonists is not known. In total, according to the company's estimates, the target population for BOTOX in this indication is around 70,000 patients, an estimate confirmed by experts.

[21] Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int. 2001; 87: 760-6.

[22] Cf. Committee's Opinion on BETMIGA of 5 February 2014.

NB: The estimate of the prevalence of overactive bladder syndrome depends on the definition of overactive bladder syndrome used in epidemiological studies. In addition, it varies in particular according to age (it increases in older subjects), the body mass index (it increases with the BMI) and sex (it is most common in women). Male urinary incontinence is little studied and poorly known.

## 011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

### ◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.